CERTAIN QUINOLINE DERIVATIVES

This application is a divisional of co-pending Application No. 09/367,227, filed on August 11, 1999, for which priority is claimed under 35 U.S.C. § 120. Application No. 09/367,227 is the U.S. national phase under 35 U.S.C. § 371 of PCT International Application No. PCT/JP98/01481 filed on March 31, 1998. The entire contents of each of the above-identified applications are hereby incorporated by reference. This application also claims priority under 35 U.S.C. § 119 to Application No. 9-98433 and 9-366764 filed in Japan on March 31, 1997 and December 26, 1997, respectively.

BACKGROUND OF THE INVENTION

This invention relates to clinically useful medicaments having a serotonin antagonism, in particular for treating, ameliorating, and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia.

Myotonia, which seriously restrains daily life, is induced by any of a number of factors or a combination thereof, for example, cervico-omo-brachial syndromes accompanying stiffness or pain in the neck, shoulder, arm, lumbar, and dorsal skeletal muscles due to abnormal posture, fatigue, changes in the backbone with ageing, etc., shoulder periarthritis accompanying inflammation in the tissues constituting the shoulder joint due to changes in the shoulder joint caused by trauma, etc., and spastic

paralysis wherein accelerated limb muscle tonus hinders voluntary movements.

In particular, spastic paralysis is a disease which accompanies limb muscle tonus, stiffening, walking difficulty, etc., and thus seriously restrains daily life.

It has been a practice to treat these diseases mainly with the use of medicaments. At the present stage, central muscle relaxants or peripheral muscle relaxants are administered to patients with these diseases. Particular examples of such central muscle relaxants include Tolperisone hydrochloride, Baclofen, Tizanidine hydrochloride, Chlorzoxazone, and Diazepam. Particular examples of such peripheral muscle relaxants include suxamethonium chloride, Pancuronium bromide, and dantrolene sodium.

Central muscle relaxants act selectively on the central nervous system so as to relax muscles. Therefore, it is expected that those action on the upper center would exhibit a more potent muscle relaxant effect. However, there arise at the same time some problems including extrapyramidal symptoms and neurologic manifestations such as sleepiness, sluggishness, and atony. No medicament capable of achieving well-balanced principal action and side effects has been known hitherto.

Diazepam, which is inherently a minor tranquilizer, is efficacious against diseases accompanying mental symptoms such

as anxiety, tension and depression. However, its effect is too potent to merely ameliorate myotonia. With the use of diazepam, therefore, spastic paralysis can be relieved but there arise some problems such as dizziness. Suxamethonium chloride and Pancuronium bromide, which are peripheral muscle relaxants, are marketed exclusively as injections, which makes the chronic administration thereof difficult. Dantrolene sodium is processed into injections and preparations for oral use and has a relatively potent muscle relaxant effect. However, it has only a low margin of safety and frequently induces muscular atony. Accordingly, it is difficult for those other than medical specialists to administer this medicine.

SUMMARY OF THE INVENTION

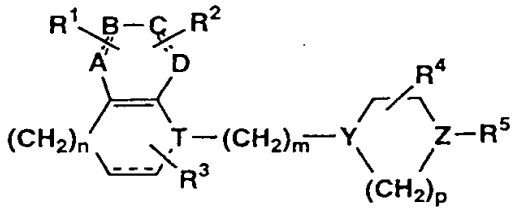
In view of the lack of a clinically useful, highly safe medicament for treating and amelioriating mytonia in spastic paralysis and the like, as discussed above, the present inventors have developed medicaments for treating, ameliorating, and preventing spastic paralysis or central muscle relaxants which have a potent effect of ameliorating myotonia while sustaining a high safety profile. It has been found that a novel class of 1,4-substituted cyclic amine derivatives represented by the following formula, and pharmacologically acceptable salts thereof, have an excellent central muscle relaxant effect while maintaining a high safety safety profile. This discovery makes

it possible to solve the above problems, thus completing the present invention.

Accordingly, the present invention aims at providing clinically useful novel medicaments which have well-balanced principal action and side effects and make it possible to overcome the problem encountering in the prior art that those acting on the upper center would exhibit a more potent muscle relaxant effect but at the same time suffer from some problems including extrapyramidal symptoms and neurologic manifestations such as sleepiness, sluggishness and weakness.

Because of the anti-serotonin effect, it is expected that the 1,4-substituted cyclic amine derivative (I) of the present invention is moreover usable in preventing, treating and ameliorating depression, emotional disorders, schizophrenia, sleep disturbance, anxiety, spinal cord injury, thrombosis, hypertension, brain circulatory disturbances, peripheral circulatory disturbances, drug addiction, etc.

The 1,4-substituted cyclic amine derivative (I) according to the present invention is represented by the following formula:



(I)

wherein A, B, C and D are the same or different from one another and each represents methine or nitrogen, provided at least two of them are methine;

the bond represented by the following formula:

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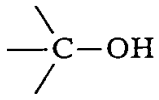
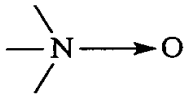
represents a single or double bond;

T represents methine or nitrogen;

Y and Z are the same or different from each other and each represents methine, nitrogen, a group represented by the following formula:



or a group represented by the following formula:



provided at least one of them represents nitrogen;

R^1 and R^2 are the same or different from each other and each represents hydrogen, halogeno, hydroxy, lower alkylsulfonylaminoalkyl, lower halogenated-alkylsulfonylaminoalkyl, 2-pyrrolidinon-1-yl, 1-hydroxy-1-(methoxypyridyl)methyl, methoxypyridylcarbonyl, 1,3-propanesultum-2-yl, lower hydroxypiperidylcarbonylalkyl, lower hydroxyalkylamidoalkyl, lower halogenated-alkylamidoalkyl, lower dihalogenated-alkylamidoalkyl, lower

heteroarylamidoalkyl, lower hydroxyalkylamidoalkyl, optionally substituted amino, nitro, lower alkyl, lower alkoxy, lower acyl, lower alkoxyalkoxy, cyano, lower alkylsulfonyl, sulfonylamido, hydroxy-lower alkyl, hydroxy-lower alkoxy, lower alkoxycarbonylamino, lower alkylsulfonylamino, N-lower alkylalkylsulfonylamino, lower acylamino, optionally substituted aminoalkyl, optionally N-substituted lower acylaminoalkyl, optionally substituted aryl, optionally substituted arylsulfonylamino, lower alkylsulfonyloxy, hydroxyiminomethyl, (2-pyrrolidon-1-yl)methyl, (2-piperidon-1-yl)methyl, optionally substituted heteroaryl, optionally substituted aralkyl, optionally substituted heteroarylalkyl, cycloalkylcarbonylaminoalkyl, optionally substituted ureido, optionally substituted ureido-lower alkyl, succinimido, (succinimido-1-yl)-lower alkyl, amido, optionally substituted carbamoyl, optionally substituted carbamoyl-lower alkyl, optionally substituted thiocarbamoyl-lower alkyl, formyl, aromatic acyl, heteroarylcarbonyl, halogenated lower alkyl, (2-imidazolidinon-1-yl)methyl, (2,4-imidazolidinedion-3-yl)methyl, (2-oxazolidon-3-yl)methyl, (glutarimido-1-yl)methyl, optionally substituted heteroarylhydroxyalkyl, cyano-lower alkyl, 1-hydroxy lower cycloalkyl, (2,4-thiazolidinedion-3-yl)methyl, optionally substituted 4-

piperidylmethyl, heteroarylacyl, pyrrolidinylcarbonyl-lower alkyl, optionally substituted aminosulfonylalkyl, carboxy-lower alkyl or lower alkylamidoalkyl; or alternatively R^1 and R^2 together may form optionally substituted alicycle, optionally substituted heterocycle or alkylenedioxy, provided these rings may be substituted;

R^3 represents hydrogen, halogeno, lower alkyl, hydroxy, hydroxy-lower alkyl, lower alkoxy, formyl, optionally substituted aralkyloxy, hydroxy-lower alkoxy, optionally substituted sulfamoyl or optionally N-substituted sulfamoyl-lower alkyl;

R^4 represents hydrogen, lower alkyl, hydroxy-lower alkyl, lower alkoxyalkyl, optionally aryl-substituted aryloxyalkyl or optionally aryl-substituted aralkyloxyalkyl;

R^5 represents lower alkyl, lower acyl, lower alkoxycarbonyl, aromatic acyl or a group represented by the following formula:

$$-Q^1-(CH_2)_s-Q^2-R^6$$

[wherein

Q^1 and Q^2 are both single bonds, or one of them is a single bond while the other represents oxygen, carbonyl, a group represented by -NHCO-, a group represented by $-NHSO_2-$ or a group represented by $>CH-R^7$ (wherein R^7 represents hydroxy, lower alkyl or halogeno):

s represents 0 or an integer of 1 to 6; and

R^6 represents optionally substituted aryl, optionally substituted heteroaryl, optionally substituted benzoheteroaryl, 1,4-benzodioxanyl, 1,3-benzodioxolyl, benzothiazolyl or cyano];

n represents 0 or an integer of 1 to 3;

m represents 0 or an integer of 1 to 6; and

p represents an integer of 1 to 3.

DETAILED DESCRIPTION OF THE INVENTION

The term "halogeno" as used in the above definition particularly means chloro, fluoro, bromo and iodo.

The term "optionally substituted amino" particularly means amino optionally substituted by lower alkyl, optionally substituted aryl, etc.

The term "lower alkyl" particularly means C_{1-6} alkyl such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, pentyl and hexyl. The term "lower alkoxy" particularly means those consisting of the above lower alkyl and oxygen bonded thereto such as methoxy, ethoxy and propoxy. The term "lower acyl" particularly means those consisting of lower alkoxy and carbonyl bonded thereto such as acetyl, propionyl and butyryl. The term "lower alkoxyalkoxy" particularly means the above lower alkoxy further substituted by lower alkoxy such as methoxymethoxy, methoxyethoxy and methoxypropoxy. The term

"lower alkylsulfonyl" particularly means the above lower alkyl bonded to sulfonyl (-SO_2-) such as methanesulfonyl and ethanesulfonyl. The term "sulfonylamido" means those represented by the formula (-SO_2NH_2). The term "hydroxy-lower alkyl" particularly means the above lower alkyl substituted by one or more hydroxy groups such as hydroxymethyl, hydroxyethyl and hydroxypropyl. The term "lower alkylsulfonylamino" particularly means the above lower alkyl bonded to sulfonylamino (-$SO_2N<$) such as methanesulfonylamino, ethanesulfonylamino, propanesulfonylamino, butanesulfonylamino and N-methylmethanesulfonylamino. The term "lower acylamino" particularly means amino bonded to lower (C_{2-6}) fatty acids such as acetamido, propionamido and butyrylamido.

The term "optionally N-substituted lower acylaminoalkyl" particularly means the above lower acyl bonded to amino-lower alkyl such as acetamidomethyl, acetamidoethyl, propionamidomethyl and butrylamidomethyl which may be further N-substituted by lower alkyl, etc.

The term "optionally substituted arylsulfonylamino" particularly means aryl bonded to sulfonylamino (-SO_2NH-) and optionally further substituted such as benzenesulfonylamino and toluenesulfonylamino. The term "lower alkylsulfonyloxy" particularly means the above lower alkyl bonded to sulfonyloxy

(-SO_3-). The term "optionally substituted aminoalkyl" particularly means amino bonded to the above lower alkyl which may be further N-substituted by lower alkyl, lower alkylsulfonyl, etc.

The term "optionally substituted aryl" particularly means optionally substituted phenyl, optionally substituted naphthyl, etc. Preferable substituents are a halogen or a lower alkoxy, and further preferable are fluorine, chlorine and methoxy. And plural substituents may be used, which are the same as or different from one another. The term "optionally substituted heteroaryl" particularly means optionally substituted pyridyl, pyrazyl, pyrimidyl, pyrrolyl, imidazolyl, pyrazolyl, quinolyl, isoquinolyl, furyl, thienyl, thiazolyl, etc. The term "optionally substituted aralkyl" particularly means optionally substituted benzyl, phenethyl, phenylpropyl, etc. The term "optionally substituted heteroarylalkyl" particularly means optionally substituted pyridylmethyl, pyridylethyl, pyrazylethyl, pyridonemethyl, pyrrolidonemethyl, pyrrolylmethyl, imidazolylmethyl, triazolylmethyl, thiazolylmethyl, etc. The term "cycloalkylcarbonylaminoalkyl" means carbonylaminoalkyl bonded to C_{3-8} cycloalkyl.

The term "optionally substituted carbamoyl-lower alkyl" particularly means, for example, carbamoylmethyl (H_2NCOCH_2-)

optionally N-substituted by lower alkyl, cycloalkyl, lower hydorxyalkyl, lower dihydroxyalkyl, lower carbamoylalkylcarbamoylalkyl, lower dialkylaminoalkyl, lower cyanoalkyl, lower alkoxyalkyl, lower halogenated-alkyl, etc. at the 1 or 2 position. The term "optionally substituted thiocarbamoyl-lower alkyl" particularly means, for example, thiocarbamoylmethyl (H_2NCSCH_2-) optionally N-substituted by lower alkyl, etc.

The term "heteroarylcarbonyl" particularly means pyridylcarbonyl, pyrrolylcarbonyl, thaizolylcarbonyl, etc. The term "halogenated lower alkyl" means lower alkyl substituted with halogeno such as chloromethyl, fluoromethyl, fluoroethyl, etc.

The term "optionally substituted heteroarylhydroxyalkyl" particularly means pyridylhydroxymethyl, thiazolylhydroxymethyl, pyrimidylhydroxymethyl, pyrrolylhydroxymethyl, etc.

More particularly, the 1,4-substituted cyclic amine derivatives (I) of the present invention are exemplified by the following compounds, though the present invention is not restricted thereto:

(1) 1-[1-(4-fluorophenyl)piperidin-4-yl]indoline,

(2) 1-[1-(4-fluorobenzyl)piperidin-4-yl]indoline,

(3) 1-(1-phenethylpiperidin-4-yl)indoline,

(4) 1-[1-(4-bromophenethyl)piperidin-4-yl]indoline,

(5) 1-[1-(3-chlorophenethyl)piperidin-4-yl]indoline,

(6) 1-[1-(4-chlorophenethyl)piperidin-4-yl]indoline,

(7) 1-[1-(2-fluorophenethyl)piperidin-4-yl]indoline,

(8) 1-[1-(3-fluorophenethyl)piperidin-4-yl]indoline,

(9) 1-[1-(4-fluorophenethyl)piperidin-4-yl]indoline,

(10) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]indoline,

(11) 1-[1-(3,4-difluorophenethyl)piperidin-4-yl]indoline,

(12) 1-[1-(3,5-difluorophenethyl)piperidin-4-yl]indoline,

(13) 1-[1-(4-fluorophenylpropyl)piperidin-4-yl]indoline,

(14) 1-{1-[2-(4-fluorophenyl)propyl]piperidin-4-yl}indoline,

(15) 1-[1-(4-fluorophenylbutyl)piperidin-4-yl]indoline,

(16) 1-[1-(4-fluorophenethyl)piperidin-4-yl]methylindoline,

(17) 1-{2-[1-(4-fluorophenethyl)piperidin-4-yl]ethyl}indoline,

(18) 1-[1-(4-methoxyphenethyl)piperidin-4-yl]indoline,

(19) 1-[1-(3-methoxyphenethyl)piperidin-4-yl]indoline,

(20) 1-[1-(4-hydroxyphenethyl)piperidin-4-yl]indoline,

(21) 1-[1-(4-cyanophenethyl)piperidin-4-yl]indoline,

(22) 1-[1-(3-hydroxymethylphenethyl)piperidin-4-yl]indoline,

(23) 1-[1-(4-hydroxymethylphenethyl)piperidin-4-

yl]indoline,

(24) 1-{1-[4-(2-hydroxyethyl)phenethyl]piperidin-4-yl]indoline,

(25) 1-{4-[(1-hydroxyethyl)phenethyl]piperidin-4-yl}indoline,

(26) 1-{1-[4-(2-hydroxyethoxy)phenethyl]piperidin-4-yl}indoline,

(27) 1-[1-(4-trifluoromethylphenethyl)piperidin-4-yl]indoline,

(28) 1-[1-(4-methanesulfonylphenethyl)piperidin-4-yl]indoline,

(29) 1-[1-(4-nitrophenethyl)piperidin-4-yl]indoline,

(30) 1-[1-(4-aminophenethyl)piperidin-4-yl]indoline,

(31) 1-[1-(4-methylsulfonylaminophenethyl)piperidin-4-yl]indoline and 1-{1-[4-bis(methylsulfonyl)aminophenethyl]piperidin-4-yl}indoline,

(32) 1-[1-(4-acetamidophenethyl)piperidin-4-yl]indoline,

(33) 1-[1-(4-ethylaminophenethyl)piperidin-4-yl]indoline,

(34) 1-[1-(4-hydroxyiminomethylphenethyl)piperidin-4-yl]indoline,

(35) 1-[1-(4-aminomethylphenethyl)piperidin-4-yl]indoline,

(36) 1-[1-(4-acetamidomethylphenethyl)piperidin-4-yl]indoline,

(37) 1-[1-(4-chloroacetamidomethylphenethyl)piperidin-4-

yl]indoline,

(38) 1-[1-(4-methanesulfonylaminomethylphenethyl)-piperidin-4-yl]indoline,

(39) 1-[1-(4-propionylaminomethylphenethyl)piperidin-4-yl]-3-methylindoline,

(40) 1-[1-(4-carbamoylphenethyl)piperidin-4-yl]indoline,

(41) 1-[1-(4-N-isopropylcarbamoylmethylphenethyl)piperidin-4-yl]indoline,

(42) 1-[1-(4-sulfamoylphenethyl)piperidin-4-yl]indoline,

(43) 1-{3-[(2-hydroxyethoxy)phenethyl]piperidin-4-yl}indoline,

(44) 1-{1-[4-(2-dimethylaminoethoxy)phenethyl]piperidin-4-yl}indoline,

(45) 1-{1-[3,4-di(hydroxymethyl)phenethyl]piperidin-4-yl}indoline,

(46) 1-{1-[3,4-(methylenedioxy)phenethyl]piperidin-4-yl}indoline,

(47) 1-{1-[2-(4-chlorophenylsulfonylamino)ethyl]-piperidin-4-yl}indoline,

(48) 1-{1-[2-(4-methoxyphenylsulfonylamino)ethyl]-piperidin-4-yl}indoline,

(49) 1-{1-[2-(4-pyridyl)ethyl]piperidin-4-yl}indoline,

(50) 1-{1-[2-(2-pyridyl)ethyl]piperidin-4-yl}indoline,

(51) 1-{1-[2-(3-pyridyl)ethyl]piperidin-4-yl}indoline,

(52) 1-{1-[2-(2-methoxy-5-pyridyl)ethyl]piperidin-4-yl}indoline,

(53) 1-{1-[2-(3-methoxypyridin-5-yl)ethyl]piperidin-4-yl}indoline,

(54) 1-{1-[2-(2-cyanopyridin-5-yl)ethyl]piperidin-4-yl}indoline,

(55) 1-{1-[2-(2-hydroxymethylpyridin-5-yl)ethyl]-piperidin-4-yl}indoline,

(56) 1-{1-[2-(3-hydroxymethylpyridin-5-yl)ethyl]-piperidin-4-yl}indoline,

(57) 1-[1-(2,6-difluoro-3-pyridylethyl)piperidin-4-yl]indoline,

(58) 1-{1-[2-(2-thienyl)ethyl]piperidin-4-yl}indoline,

(59) 1-{1-[2-(3-thienyl)ethyl]piperidin-4-yl}indoline,

(60) 1-[1-(2-thiazolylethyl)piperidin-4-yl]indoline,

(61) 1-[1-(4-methyl-5-thiazolylethyl)piperidin-4-yl]indoline,

(62) 1-{1-[(indol-3-yl)ethyl]piperidin-4-yl}indoline,

(63) 1-{1-[2-(6-benzothiazolyl)ethyl]piperidin-4-yl}indoline,

(64) 1-[1-(5-methoxy-2-thienyl)ethylpiperidin-4-yl]indoline,

(65) 1-[1-(2-methoxy-5-thiazolyl)ethylpiperidin-4-yl]indoline,

(66) 1-[1-(2-cyano-5-thiazolyl)ethylpiperidin-4-yl]indoline,

(67) 1-(1-pyrazinylethylpiperidin-4-yl)indoline,

(68) 1-{1-[2-(4-bromopyrazol-1-yl)ethyl]piperidin-4-yl}indoline,

(69) 1-{1-[3-(4-fluorophenoxy)propyl]piperidin-4-yl}indoline,

(70) 1-{1-[3-(4-hydroxymethylphenoxy)propyl]piperidin-4-yl}indoline,

(71) 1-{1-[3-(4-hydroxyethylphenoxy)propyl]piperidin-4-yl}indoline,

(72) 1-{1-[4-(4-fluorophenyl)-4-oxobutyl]piperidin-4-yl}indoline,

(73) 1-{1-[4-(4-fluorophenyl)-4-hydroxybutyl]piperidin-4-yl}indoline,

(74) 1-[1-(phthalimido-1-yl)ethylpiperidin-4-yl]indoline,

(75) 1-[1-(4-fluorobenzamido)ethylpiperidin-4-yl]indoline,

(76) 1-{1-[1-(3,4-dimethoxyphenyl)propan-2-yl]piperidin-4-yl}indoline,

(77) 1-{1-[(1,4-benzodioxan-2-yl)methyl]piperidin-4-yl}indoline,

(78) 1-{1-[3-(3,4-methylenedioxyphenoxy)propyl]piperidin-4-yl}indoline,

(79) 1-[1-(4-fluorophenethyl)-3-methylpiperidin-4-

yl]indoline,

(80) 1-(1-benzyl-3-hydroxymethylpiperidin-4-yl)indoline,

(81) 1-[1-(4-fluorophenethyl)-3-hydroxymethylpiperidin-4-yl]indoline,

(82) 1-[1-(4-fluorophenethyl)-3-hydroxymethylpiperidin-4-yl]indoline,

(83) 1-[2-(4-acetamidomethylphenyl)ethyl]-4-(indan-1-yl)piperidin-1-oxide,

(84) 1-[1-ethyl-3-(4-fluorophenoxymethyl)piperidin-4-yl]indoline,

(85) 1-[1-ethyl-3-(4-fluorobenzyloxymethyl)piperidin-4-yl]indoline,

(86) 1-[1-ethyl-3-(4-fluorobenzyloxymethyl)piperidin-4-yl]indoline,

(87) 1-(1-acetylpiperidin-4-yl)indoline-7-carbaldehyde,

(88) ~~1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-~~ bromoindoline,

(89) ~~1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-~~ hydroxymethylindoline,

(90) ~~1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-~~ aminomethylindoline,

(91) 1-(1-benzylpiperidin-4-yl)-6-bromoindoline,

(92) 1-(1-benzylpiperidin-4-yl)-6-fluoroindoline,

(93) 1-(1-benzylpiperidin-4-yl)-6-formylindoline,

(94) 1-(1-benzylpiperidin-4-yl)-6-hydroxyiminomethyl-indoline,

(95) 1-(1-benzylpiperidin-4-yl)-6-aminomethylindoline,

(96) 1-(1-benzylpiperidin-4-yl)-6-acetamidomethyl-indoline,

(97) 1-[1-(4-methoxyphenethyl)piperidin-4-yl]-6-acetamidomethylindoline,

(98) 1-[1-(4-chlorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline,

(99) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-5-methoxyindoline,

(100) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline,

(101) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline,

(102) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloroindoline,

(103) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoroindoline,

(104) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyindoline,

(105) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-4-methoxyindoline,

(106) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-

methoxyindoline,

(107) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-methoxyindoline,

(108) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6,7-dimethoxyindoline,

(109) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-nitroindoline,

(110) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminoindoline,

(111) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methylaminoindoline,

(112) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-ethylaminoindoline,

(113) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-isopropylaminoindoline,

(114) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-dimethylaminoindoline,

(115) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidoindoline,

(116) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonylaminoindoline,

(117) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-ethanesulfonylaminoindoline,

(118) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-

propanesulfonylaminoindoline,

(119) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-fluorobenzenesulfonylamino)indoline,

(120) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N-methylmethanesulfonylamino)indoline,

(121) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyethoxyindoline,

(122) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonyloxyindoline,

(123) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-hydroxyethoxyindoline,

(124) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanoindoline,

(125) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylindoline,

(126) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-pyrrolylcarbonyl)indoline,

(127) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetylindoline,

(128) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonylindoline,

(129) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-thiocarbamoylmethylindoline,

(130) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-

formylindoline,

(131) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyiminomethylindoline,

(132) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminomethylindoline,

(133) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline,

(134) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline,

(135) 1-[1-(3-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline,

(136) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindoline,

(137) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxyethyl)indoline,

(138) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxypropyl)indoline,

(139) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxy-1-methylethyl)indoline,

(140) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxycyclobutyl)indoline,

(141) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxycyclopentyl)indoline,

(142) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-

chloromethylindoline,

(143) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoromethylindoline,

(144) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-fluoroethyl)indoline,

(145) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanomethylindoline,

(146) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carboxymethylindoline,

(147) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylmethylindoline,

(148) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(methylcarbamoylmethyl)indoline,

(149) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(ethylcarbamoylmethyl)indoline,

(150) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(n-propylcarbamoylmethyl)indoline,

(151) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(isopropylcarbamoylmethyl)indoline,

(152) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(isobutylcarbamoylmethyl)indoline,

(153) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(t-butylcarbamoylmethyl)indoline,

(154) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-

(cyclopropylcarbamoylmethyl)indoline,

(155) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(tetramethylenecarbamoylmethyl)indoline,

(156) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-propionylaminomethylindoline,

(157) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(n-butyryl)aminomethylindoline,

(158) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-isobutyrylaminomethylindoline,

(159) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyclopropanecarboxamidomethylindoline,

(160) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methylsulfonylaminomethylindoline,

(161) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-ureidomethylindoline,

(162) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N-methylaminomethylindoline,

(163) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N-methylacetamidomethylindoline,

(164) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N-methylsulfamoylmethyl)indoline,

(165) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-acetamidoethyl)indoline,

(166) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-

acetamidoethylindoline,

(167) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(piperidin-4-yl)methyl]indoline,

(168) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(1-acetylpiperidin-4-yl)methyl]indoline,

(169) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(1-ethylpiperidin-4-yl)methyl]indoline,

(170) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(1-methylpiperidin-4-yl)methyl]indoline,

(171) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-pyridyl)indoline,

(172) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-thiazolyl)indoline,

(173) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-methylpyrrol-2-yl)indoline,

(174) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)methyl]indoline,

(175) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(2-pyridyl)methyl]indoline,

(176) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(3-pyridyl)methyl]indoline,

(177) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(3-pyridyl)methyl]indoline,

(178) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-

hydroxy-4-pyridylmethyl)indoline,

(179) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-pyridylmethyl)indoline,

(180) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-pyridylcarbonyl)indoline,

(181) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-pyridyl)ethyl]indoline,

(182) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(2-pyridyl)ethyl]indoline,

(183) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-pyridylcarbonyl)indoline,

(184) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-3-yl)methyl]indoline,

(185) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(2-methoxypyridin-3-yl)methyl]indoline,

(186) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-6-yl)methyl]indoline,

(187) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(2-methoxypyridin-6-yl)methyl]indoline,

(188) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-methoxypyridin-5-yl)methyl]indoline,

(189) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(2-methoxypyridin-5-yl)methyl]indoline,

(190) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-

hydroxy-1-(2-pyridon-5-yl)methyl]indoline,

(191) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-dimethylaminopyridin-5-yl)methyl]indoline,

(192) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-chloropyridin-5-yl)methyl]indoline,

(193) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(2-thiazolyl)-1-hydroxymethyl]indoline,

(194) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-thiazolylcarbonyl)indoline,

(195) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(4-thiazolyl)-1-hydroxymethyl]indoline,

(196) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(5-thiazolyl)-1-hydroxymethyl]indoline,

(197) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(pyrimidin-2-yl)methyl]indoline,

(198) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(pyrimidin-5-yl)methyl]indoline,

(199) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-hydroxy-1-(2-pyrrolyl)methyl]indoline,

(200) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N,N-dimethylaminomethylindoline,

(201) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-fluorophenyl)indoline,

(202) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-

pyrrolidon-1-yl)methylindoline,

(203) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-piperidon-1-yl)methylindoline,

(204) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(succinimido-1-yl)methylindoline,

(205) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(glutarimido-1-yl)methylindoline,

(206) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-imidazolidonyl)methylindoline,

(207) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2,4-imidazolidinedion-3-yl)methylindoline,

(208) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-oxazolidon-3-yl)methylindoline,

(209) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2,4-thiazolidinedion-3-yl)methylindoline,

(210) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(pyrrol-1-yl)methylindoline,

(211) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(imidazol-1-yl)methylindoline,

(212) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,2,3-triazol-1-yl)methylindoline and

1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,2,3-triazol-2-yl)methylindoline,

(213) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,2,4-

triazol-2-yl)methylindoline,

(214) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-thiazolyl)methylindoline,

(215) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-(4-methoxybenzyl)indoline,

(216) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-methylindoline,

(217) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-5-chloro-6-aminoindoline,

(218) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-5-chloro-6-methanesulfonylaminoindoline,

(219) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-5-chloro-6-methoxyindoline,

(220) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-aminoindoline,

(221) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-methanesulfonylaminoindoline,

(222) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-acetamidoindoline,

(223) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-bromoindoline,

(224) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline,

(225) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-

carbamoylmethylindoline,

(226) 1-{1-[3-(4-fluorophenyl)propyl]piperidin-4-yl}-6-acetamidomethylindoline,

(227) 1-{1-[4-(4-fluorophenyl)butyl]piperidin-4-yl}-6-acetamidomethylindoline,

(228) 1-[1-(4-methoxyphenethyl)piperidin-4-yl]-6-methoxyindoline,

(229) 1-[1-(4-methoxyphenethyl)piperidin-4-yl]-6-fluoroindoline,

(230) 1-[1-(4-sulfamoylphenethyl)piperidin-4-yl]-6-methoxyindoline,

(231) 1-[1-(4-fluorophenoxypropyl)piperidin-4-yl]-6-bromoindoline,

(232) 1-[1-(4-fluorophenoxypropyl)piperidin-4-yl]-6-acetamidomethylindoline,

(233) 1-{1-[2-(6-benzothiazolyl)ethyl]piperidin-4-yl}-6-methoxyindoline,

(234) 1-[1-(4-fluorophenethyl)piperidin-4-yl]thiazolo[5,4-f]indoline,

(235) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-aminothiazolo[5,4-f]indoline,

(236) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-hydroxy-(4a,7a)-cyclohexanoindoline and

1-[1-(4-fluorophenethyl)piperidin-4-yl]-4-hydroxy-(3b,6a)-

cyclohexanoindoline,

(237) 1-(1-methylpiperidin-4-yl)-6-(4-fluorobenzene-sulfonylamino)indoline,

(238) 1-(1-ethylpiperidin-4-yl)-6-(4-fluorobenzene-sulfonylamino)indoline,

(239) 1-(1-ethylpiperidinyl)-4-(4-fluorophenyl)indoline,

(240) 1-(1-ethylpiperidin-4-yl)-3-(4-fluorophenyl)-indoline,

(241) 1-(1-ethylpiperidin-4-yl)-3-(4-methoxyphenyl)-indoline,

(242) 1-(1-ethylpiperidin-4-yl)-3-(4-methoxybenzyl)-indoline,

(243) 1-[(1-ethylpiperidin-4-yl)methyl]-3-(4-methoxy-benzyl)indoline,

(244) 1-(1-ethylpiperidin-4-yl)-3-(4-fluorobenzyl)-indoline,

(245) 1-(1-ethylpiperidin-4-yl)-3-(3-pyridylmethyl)-indoline,

(246) 1-(1-ethylpiperidin-4-yl)-3-(3-methoxyphenethyl)-indoline,

(247) 1-(1-ethylpiperidin-4-yl)-3-(3-fluorophenethyl)-indoline,

(248) 1-[1-(4-fluorophenethyl)piperidin-4-yl]indan,

(249) 1-[1-(4-methoxyphenethyl)piperidin-4-yl]indan,

(250) 1-{4-[2-(4-fluorophenyl)ethyl]piperazin-1-yl}-6-methoxyindan,

(251) 1-(4-ethylpiperazin-1-yl)-6-methoxyindan,

(252) 1-(4-ethylpiperazin-1-yl)-2-ethoxycarboxyamino-indan,

(253) 1-(4-ethylpiperazin-1-yl)-2-methylaminoindan,

(254) 1-(4-ethylpiperazin-1-yl)-2-[methyl-(4-trifluorobenzyl)amino]indan,

(255) 7-[4-hydroxy-1-(4-fluorophenethyl)piperidin-4-yl]-5,6-dihydro-7H-pyrindine,

(256) 7-[1-(4-fluorophenethyl)piperidin-4-ylidene]-5,6-dihydropyrindine,

(257) 7-[1-(4-fluorophenethyl)piperidin-4-yl]-5,6-dihydro-7H-pyrindine,

(258) 7-[4-(4-fluorophenethyl)piperazin-1-yl]-5,6-dihydro-7H-pyrindine,

(259) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloro-7-azaindoline,

(260) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-7-azaindoline,

(261) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoro-7-azaindoline,

(262) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-chloro-7-azaindoline,

(263) 1-[1-(4-methoxyphenethyl)piperidin-4-yl]-6-chloro-7-azaindoline,

(264) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-azaindoline,

(265) 5-[1-(4-fluorophenethyl)piperidin-4-ylidene]-7-methyl-5,6-dihydrocyclopentapyrazine,

(266) 5-[1-(4-fluorophenethyl)piperidin-4-yl]-7-methyl-5,6-dihydro-5H-cyclopentapyrazine,

(267) 1-{1-[2-(4-methoxyphenyl)ethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(268) 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(269) 1-[1-(4-cyanopropyl)piperidin-4-yl]-7-methoxy-1,2,3,4-tetrahydroquinoline,

(270) 1-{1-[2-(2-thienyl)ethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(271) 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-7,8-dimethoxy-1,2,3,4-tetrahydroquinoline,

(272) 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-7,8-methylenedioxy-1,2,3,4-tetrahydroquinoline,

(273) 1-{1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}-7-methoxy-8-methyl-1,2,3,4-tetrahydroquinoline,

(274) 1-{1-[2-(4-fluorophenyl)-2-oxoethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(275) 1-{1-[2-(4-fluorophenyl)-2-hydroxyethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(276) 1-{1-[2-(4-fluorophenyl)-2-fluoroethyl]piperidin-4-yl}-7-methoxy-1,2,3,4-tetrahydroquinoline,

(277) 1-[2-(4-fluorophenyl)ethyl]-4-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)piperidine,

(278) 1-[2-(4-fluorophenyl)ethyl]-4-[6-(2-hydroxy)ethoxy-1,2,3,4-tetrahydronaphthalen-1-yl]piperidine,

(279) trans-1-(4-ethylpiperazin-1-yl)-7-methoxy-2-(4-trifluoromethylphenoxy)-1,2,3,4-tetrahydronaphthalene,

(280) 1-{4-[2-(4-fluorophenyl)ethyl]piperazin-1-yl}-7-methoxy-1,2,3,4-tetrahydronaphthalene,

(281) 1-{4-[2-(4-fluorophenyl)-2-oxoethyl]piperazin-1-yl}-7-methoxy-1,2,3,4-tetrahydronaphthalene,

(282) 1-(4-fluorophenethyl)-4-(2-methoxybenzocycloheptan-9-yl)piperazine,

(283) 5-{4-[2-(4-fluorophenyl)ethyl]piperazin-1-yl}-5,6,7,8-tetrahydroisoquinoline,

(284) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-5,6-methylenedioxyindoline,

(285) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole,

(286) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N-isopropylcarbamoylmethyl)indole,

(287) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-methylpyrrol-2-yl)indole,

(288) 1-[1-(4-acetamidomethylphenethyl)piperidin-4-yl]indole,

(289) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanoindole,

(290) 1-[1-(4-fluorophenethyl)-3-methylpiperidin-4-yl]indole,

(291) 1-[1-(4-fluorophenethyl)homopiperidin-4-yl]-6-methoxyindoline,

(292) 1-[1-(4-fluorophenethyl)pyrrolidin-3-yl]-6-methoxyindoline,

(293) 3,3-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline,

(294) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(ethylcarbamoylmethyl)indole,

(295) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[N-(cyclopropylcarbamoyl)methyl]indole,

(296) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[N-(isobutylcarbamoyl)methyl]indole,

(297) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(n-propylcarbamoylmethyl)indole,

(298) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(tetramethylenecarbamoylmethyl)indole,

(299) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-carbamoylmethylindole,

(300) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-hydroxyethyl)carbamoylmethylindole,

(301) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-dimethylcarbamoylmethylindole,

Sub A6) ~~(302) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-~~ hydroxypiperidin-1-ylcarbonylmethyl)indole,

(303) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[bis(2-hydroxyethyl)carbamoylmethyl]indole,

(304) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,3-dihydroxypropan-2-yl)carbamoylmethylindole,

(305) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylmethylindole,

(306) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(carbamoylmethyl)carbamoylmethylindole,

(307) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-dimethylaminoethyl)carbamoylmethylindole,

(308) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyanomethylcarbamoylmethylindole,

(309) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-methoxyethyl)carbamoylmethylindole,

(310) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-fluoroethyl)carbamoylmethylindole,

(311) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(ethylcarbamoyl)ethyl]indole,

(312) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(pyrrolidin-1-yl)ethyl]carbamoylmethylindole,

(313) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(morpholin-4-yl)ethyl]carbamoylmethylindole,

(314) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(pyridin-4-yl)methylcarbamoylmethylindole,

(315) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[2-(pyridin-2-yl)ethyl]carbamoylmethylindole,

(316) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methylcarbamoylmethylindole,

(317) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-methoxypyridin-5-ylcarbonyl)indole,

(318) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(2-methoxypyridin-5-yl)hydroxymethyl]indole,

(319) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxyproyl)indole,

(320) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxy-1-methylethyl)indoline,

(321) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-hydroxypropyl)indole,

(322) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonamidomethylindole,

(323) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-isopropylsulfonamidomethylindole,

(324) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-n-propylsulfonamidomethylindole,

(325) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-chloropropyl)sulfonamidomethylindole,

(326) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,3-propanesultam-2-yl)methylindole,

(327) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-propionylaminomethylindole,

(328) 3-chloro-1-[1-(4-fluorophenethyl)-piperidin-4-yl]-6-acetamidomethylindole,

(329) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(4-hydroxybutyroylamidomethyl)indole,

(330) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyethoxyindole,

(331) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonylindole,

(332) 1-[1-(2,6-difluoro-3-pyridylethyl)piperidin-4-yl]indole,

(333) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoroindole,

(334) 1-[1-(4-fluorophenethyl)piperidin-4-yl]thiazolo-[5,4-f]indole,

(335) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N-methylmethanesulfonylamino)indole,

(336) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonyloxyindole,

(337) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylindole,

(338) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N-methylsulfamoylmethyl)indole,

(339) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidoindole,

(340) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,2-dihydroxypropan-3-yl)carbamoylmethylindole,

(341) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(pyridin-2-yl)methylcarbamoylmethylindole,

(342) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-methylcarbamoylmethylindole,

(343) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-(1-acetylpiperidin-4-yl)methylcarbamoylmethylindole,

(344) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-ethylcarbamoylmethylindole,

(345) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-ethylpiperidin-4-yl)methylcarbamoylmethylindole,

(346) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-(2-hydroxyethyl)carbamoylmethylindole,

(347) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1,3-dioxolan-2-ylmethyl)carbamoylmethylindole,

(348) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-aminomethylindole,

(349) 1-[1-(4-chlorophenethyl)piperidin-4-yl]-6-acetamidomethylindole,

(350) 1-[1-(3-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole,

(351) 1-[1-(4-methoxyphenethyl)piperidin-4-yl]-6-acetamidomethylindole,

(352) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole,

(353) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2,4-imidazolidinedion-3-yl)methylindole,

(354) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-isobutyrylaminomethylindole,

(355) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-imidazolidonyl)methylindole,

(356) 1-{1-[4-(4-fluorophenyl)butyl]piperidin-4-yl}-6-acetamidomethylindole,

(357) 1-[1-(2,4-difluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole,

(358) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(2-pyrrolidon-1-yl)methylindole,

(359) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N-methylacetamidomethylindole,

(360) 1-{1-[3-(4-fluorophenyl)propyl]piperidin-4-yl}-6-acetamidomethylindole,

(361) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N-methylaminomethylindole,

(362) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(n-butyryl)aminomethylindole,

(363) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-cyclopropanecarboxamidomethylindole,

(364) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-hydroxyacetamidomethylindole,

(365) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-difluoroacetamidomethylindole,

(366) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-fluoroacetamidomethylindole,

(367) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-chloropropionylamino)methylindole,

(368) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-imidazocarbonylaminomethylindole,

(369) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-hydroxypropionylamino)methylindole,

(370) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-formyl-6-acetamidomethylindole,

(371) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-hydroxyimino-6-acetamidomethylindole,

(372) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-3-hydroxymethyl-6-acetamidomethylindole,

(373) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-chloroacetamidomethylindole,

(374) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoacetamidomethylindole,

(375) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(N,N-dimethylaminoacetamido)methylindole,

(376) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[(piperidin-1-yl)acetamido]methylindole,

(377) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-bromopropionylamino)methylindole,

(378) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-N,N-dimethylaminopropionyl)aminomethylindole,

(379) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[3-(piperidin-1-yl)propionylamino]methylindole,

(380) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-propionylaminomethylindole,

(381) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-fluoroacetamidomethylindole,

(382) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-(3-hydroxypropionylamino)methylindole,

(383) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-hydroxyacetamidomethylindole,

(384) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxycarbonylaminomethylindole,

(385) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N,N-dimethylaminocarbonylaminomethylindole,

(386) 1-{1-[2-(3-pyridyl)ethyl]piperidin-4-yl}-6-acetamidomethylindole,

(387) 3-cyano-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole,

(388) 1-{4-[(1-hydroxyethyl)phenethyl]piperidin-4-yl}-6-acetamidomethylindole,

(389) 1-[1-(4-bromophenethyl)piperidin-4-yl]-6-acetamidomethylindole,

(390) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-formylindole,

(391) 1-[1-(2-fluorophenethyl)piperidin-4-yl]-6-hydroxymethylindole,

(392) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxyethyl)indole,

(393) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-ureidomethylindole,

(394) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-methylureido)methylindole,

(395) 3,3-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidoindoline,

(396) 2,2-dimethyl-1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methoxyindoline and

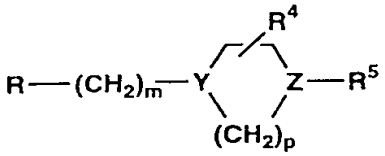
(397) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(3-methylureido)methylindole.

Although some of the 1,4-substituted cyclic amine derivatives (I) of the present invention occur as optical isomers or geometrical isomers, either one of these optical isomers or a mixture thereof may be used in the present invention without restriction. Similarly, either one of geometrical isomers or a mixture thereof may be employed herein without any restriction. In the case of polymorphic crystals, either one of the crystal forms or a mixture thereof may be used in the present invention without restriction, too. Moreover, use may be made of both anhydrides and hydrates.

The pharmacologically acceptable salts to be used in the present invention may be arbitrary salts of the 1,4-substituted cyclic amine derivatives (I) of the present invention without particular restriction. Examples thereof include inorganic acid addition salts such as hydrochlorides, sulfates, nitrates, hydrobromides, hydriodides, perchlorates and phosphates, organic acid addition salts such as oxalates, maleates, fumarates and succinates, sulfonic acid addition salts such as

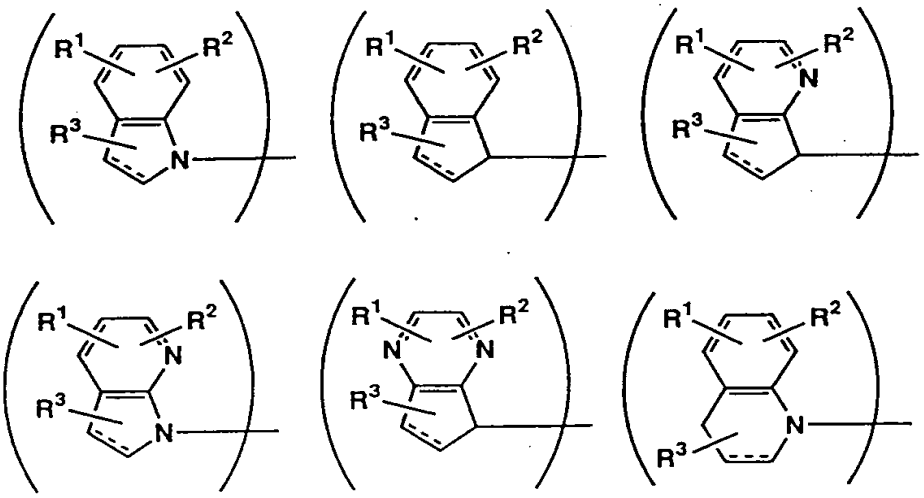
methanesulfonates, ethanesulfonates, benzenesulfonates, p-toluenesulfonates and camphorsulfonates, and amino acid addition salts. Among all, it is preferable to use hydrochlorides and oxalates thereof.

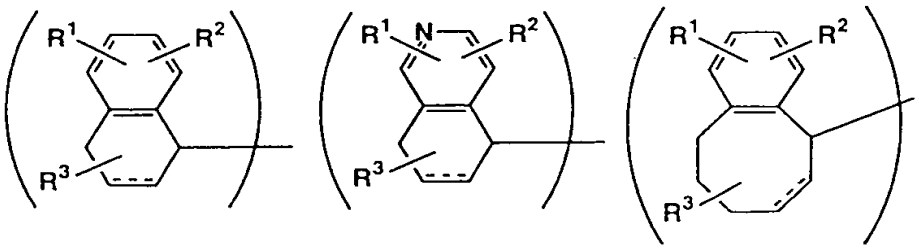
The 1,4-substituted cyclic amine derivative (II) according to the present invention is represented by the following formula:



(II)

R represents a substituent selected from among the following ones:





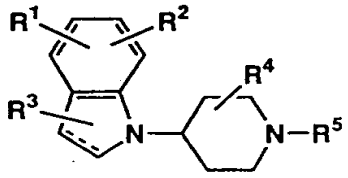
(wherein the bond represented by the following formula:

and R^1, R^2 and R^3 are each as defined above); and

R^4, R^5, Y, Z, m and p are each as defined above.

Examples of the 1,4-substituted cyclic amine derivatives (II) include compounds similar to those cited above as the examples of the 1,4-substituted cyclic amine derivatives (I), though the present invention is not restricted thereto.

The 1,4-substituted cyclic amine derivative (III) according to the present invention is represented by the following formula:



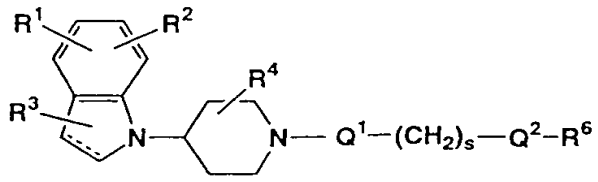
(III)

wherein the bond represented by the following formula:

and R^1, R^2, R^3, R^4 and R^5 are each as defined above.

Further, the 1,4-substituted cyclic amine derivative (IV)

of the present invention is represented by the following formula:

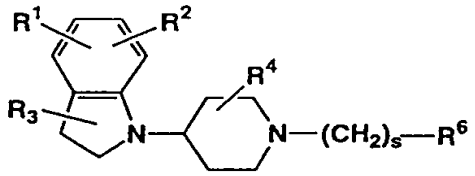


(IV)

wherein the bond represented by the following formula:

and R^1, R^2, R^3, R^4, R^6, Q^1, Q^2 and s are each as defined above.

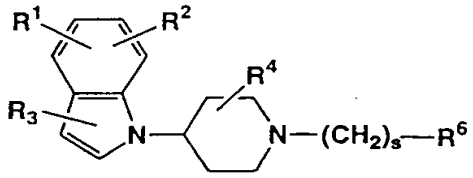
Next, the 1,4-substituted cyclic amine derivative (V) according to the present invention is represented by the following formula:



(V)

wherein R^1, R^2, R^3, R^4, R^6 and s are each as defined above.

Finally, the 1,4-substituted cyclic amine derivative (VI) according to the present invention is represented by the following formula:



(VI)

wherein R^1, R^2, R^3, R^4, R^6 and s are each as defined above.

Among the 1,4-substituted cyclic amine derivatives (I) to (VI) according to the present invention, those which are particularly preferable from the viewpoint of pharmacological effects or safety are, for example, the following ones:

(1) 1-[1-(4-acetamidomethylphenethyl)piperidin-4-yl]indoline,

(2) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-carbamoylindoline,

(3) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-methanesulfonylindoline,

(4) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindoline,

(5) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(1-hydroxyethyl)indoline,

(6) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(n-propylcarbamoylmethyl)indoline,

(7) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-(isopropylcarbamoylmethyl)indoline,

(8) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-ureidomethylindoline,

(9) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-N-methylacetamidomethylindoline,

(10) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-[1-(4-

thiazolyl)-1-hydroxymethyl]indoline, and

(11) 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-acetamidomethylindole.

The compounds of the present invention are each a highly safe one having an extremely high LD_{50}.

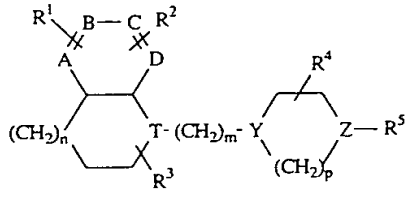
Although compounds having the indoline or indan skeleton are disclosed in WO96/23784, JP-A 8-512,299 (WO95/01976), WO97/06155, etc., these compounds are completely different in structure from the 1,4-substituted cyclic amine derivatives (I) to (VI) of the present invention.

The present invention provides the method for treating the disease which serotonin antagonism is efficacious, by administering the effective dose of the compound as set forth or pharmacologically acceptable salts thereof to a person, and the use of the compound as set forth or pharmacologically acceptable salts thereof for treating the disease which serotonin antagonism is efficacious.

The present invention includes the following mode:

(1) 1,4-Substituted cyclic amine derivatives, which the bond represented by the following formula in the formula (I):

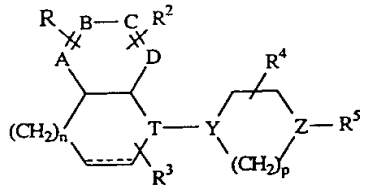
is a single bond, represented by the formula (XXI):



(XXI)

or pharmacologically acceptable salts thereof.

(2) 1,4-Substituted cyclic amine derivatives, which m is 0 in the formula (I), represented by the formula (XXII):



(XXII)

or pharmacologically acceptable salts thereof.

(3) 1,4-Substituted cyclic amine derivatives represented by the formula (I), in which m is 1 to 6 selected from the following compounds:

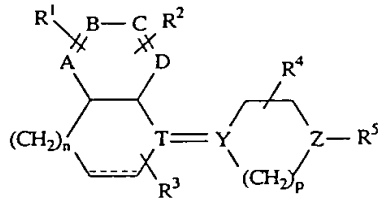
(16) 1-[1-(4-fluorophenethyl)piperidin-4-yl]methylindoline,

(17) 1-{2-[1-(4-fluorophenethyl)piperidin-4-yl]ethyl}indoline, and

(243) 1-[(1-ethylpiperidin-4-yl)methyl]-3-(4-methoxybenzyl)indoline

or pharmacologically acceptable salts thereof.

(4) 1,4-Substituted cyclic amine derivatives represented by the formula (XXIII):



(XXIII)

selected from the following compounds:

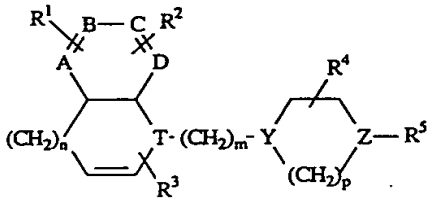
(256) 7-[1-(4-fluorophenethyl)piperidin-4-ylidene]-5,6-dihydropyrindine and

(265) 5-[1-(4-fluorophenethyl)piperidin-4-ylidene]-7-methyl-5,6-dihydrocyclopentapyrazine

or pharmacologically acceptable salts thereof.

(5) 1,4-Substituted cyclic amine derivatives, which the bond represented by the following formula in the formula (I):

is a double bond, represented by the formula (XXIV):



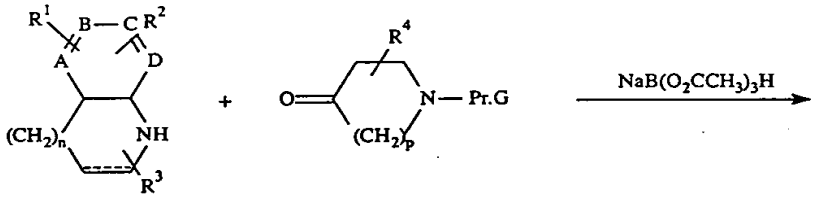
(XXIV)

or pharmacologically acceptable salts thereof.

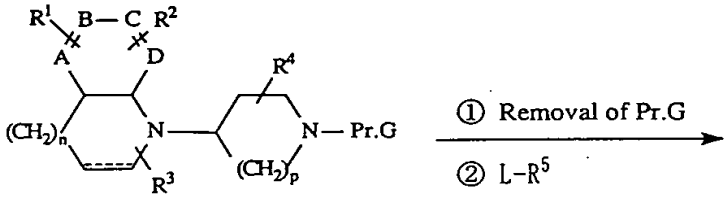
The 1,4-substituted cyclic amine derivatives (I) of the present invention can be produced by, for example, the following processes, though the present invention is not restricted thereto.

(1) The case where T = N, m = 0, Y = methine, and Z = N

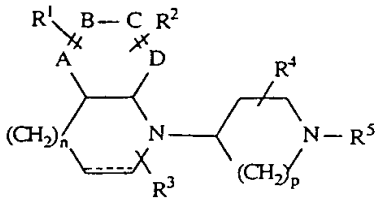
In this case, the aimed compounds can be synthesized in accordance with the conventional method of reductive amination, for example, the one described in "Shin Jikken Kagaku Koza 14-III", p. 1380 (Maruzen Co., Ltd.), by reacting a fused cyclic amine (VII) with a cyclic ketone (VIII) in the presence of a reducing agent to thereby give a 1,4-substituted cyclic amine derivative (IX), removing the protecting group therefrom if necessary, and then introducing a substituent R^5 thereinto. This reaction is represented by the following chemical reaction formula:



(VII) (VIII)



(IX)



(X)

[wherein the bond represented by the following formula:

-----

represents a single or double bond;

A, B, C, D, R^1, R^2, R^3, R^4, R^5, n and p are each as defined above;

Pr.G represents hydrogen or a protecting group; and

L represents a leaving group such as hydroxy, halogeno or methanesulfonyloxy].

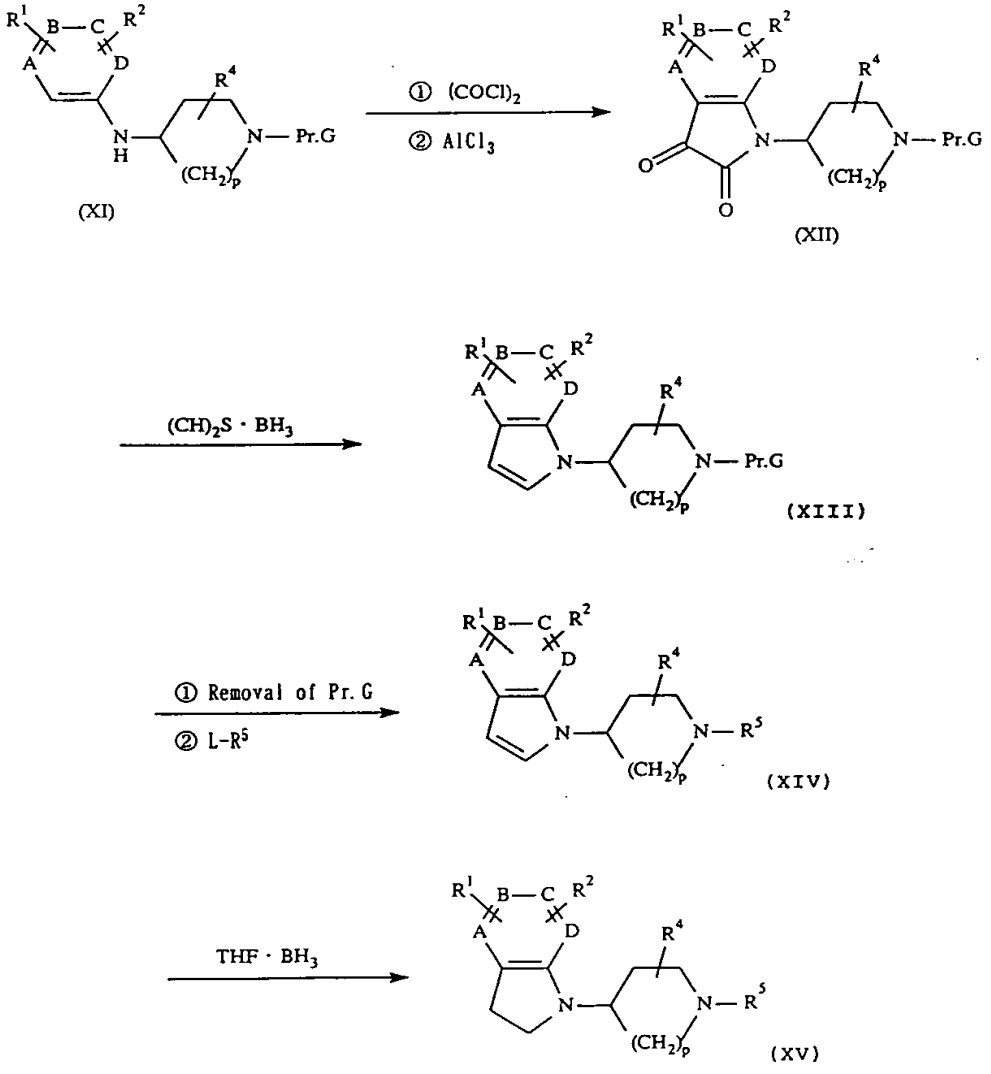
It is also possible to chemically modify the substituents R^1, R^2, R^3 and R^4 to thereby synthesize analogs of the 1,4-substituted cyclic amine derivatives.

The reducing agent to be used herein may be an arbitrary one, so long as it is one commonly employed in reductive N-alkylation. Preferable examples thereof include sodium triacetoxyborohydride, sodium cyanoborohydride and lithium aluminum hydride.

(2) The case where T = N, n = 0, m = 0, Y = methine, and Z = N

An alternative method of (1) for synthesizing, in particular, the 1,4-substituted cyclic amine derivatives (I) wherein n = 0 comprises treating the amine (XI) successively

with oxalyl chloride and aluminum chloride to thereby give a diketone (XII), reducing the same to thereby give an indole derivative (XIII), removing the protecting group therefrom if necessary, then introducing a substituent R^5 thereinto to thereby give an indole derivative (XIV), and reducing the same to thereby give an indoline derivative (XV). This reaction is represented by the following chemical reaction formula:



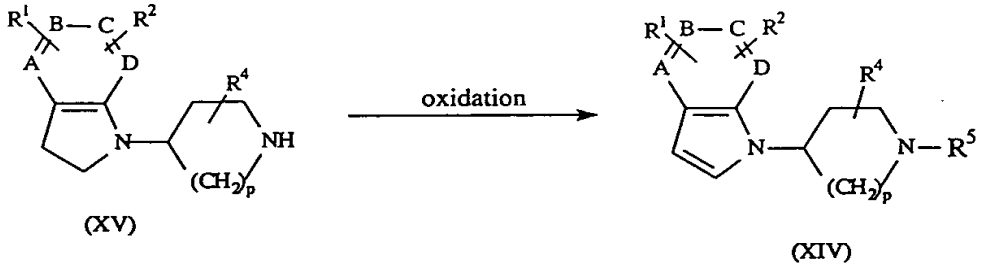
[wherein the bond represented by the following formula:

-----

and A, B, C, D, R^1, R^2, R^4, R^5, p, Pr.G and L are each as defined above.]

(3) The case of indole derivatives wherein T = N, n = 0, m = 0, Y = methine, and Z = N

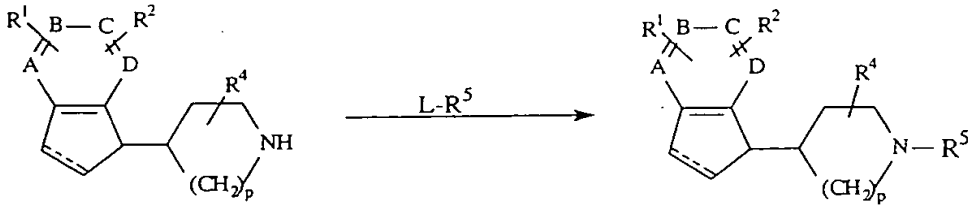
The indole derivatives (XIV) can be obtained not only by the above method (2) but also by oxidizing the indoline derivatives (XV) in a conventional manner. Although the reagent and catalyst to be used in such a case are not particularly restricted, it is preferable to use activated manganese dioxide.



(XV) (XIV)

(4) The case where T = methine, n = 0, m = 0, Y = methine, and Z = N

The aimed compounds can be synthesized by introducing a substituent R^5 into 1-(piperidin-4-yl)indan derivatives (XVI). This reaction is represented by the following chemical reaction formula:



(XVI) (XVII)

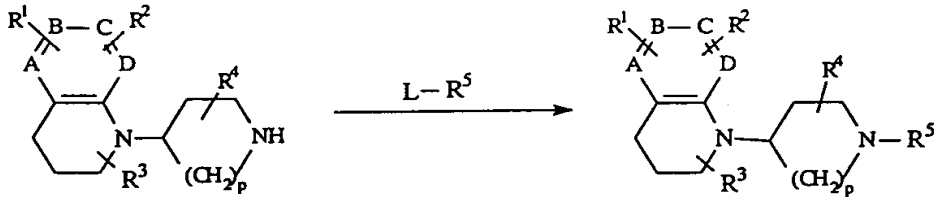
[wherein the bond represented by the following formula:

- - - - -

and A, B, C, D, R^1, R^2, R^4, R^5, p and L are each as defined above.]

(5) The case where T = N, n = 1, m = 0, Y = methine, and Z = N

The aimed compounds can be synthesized by introducing a substituent R^5 into 1-(4-piperidinyl)-1,2,3,4-tetrahydroquinoline derivatives (XVIII). This reaction is represented by the following chemical reaction formula:



(XVIII) (XIX)

[wherein the bond represented by the following formula:

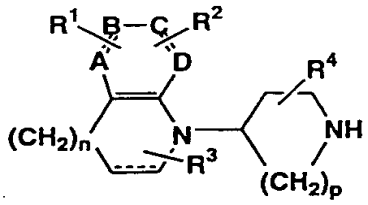
- - - - -

and A, B, C, D, R^1, R^2, R^3, R^4, R^5, p and L are each as defined above.]

Among the 1,4-substituted cyclic amine derivatives (I) according to the present invention, compounds having structures

other than those as defined in the above cases (1) to (4) can be produced by the same methods as the ones as will be described in Examples hereinafter.

To produce the 1,4-substituted cyclic amine derivatives (I) of the present invention, 4-substituted cyclic amine derivatives (XX) represented by the following formula are novel compounds which are useful as intermediates in the production of the 1,4-substituted cyclic amine derivatives (I) to (VI) having a serotonin antagonism and being clinically useful as medicaments for, in particular, treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia:



(XX)

wherein the bond represented by the following formula:

and A, B, C, D, R^1, R^2, R^3, R^4, n and p are each as defined above, provided that the case where R^1, R^2, R^3 and R^4 are all hydrogen is excluded.

More particularly speaking, the 4-substituted cyclic amine derivatives (XX) are exemplified by the following

compounds, though the present invention is not restricted thereto:

(1) 1-(piperidin-4-yl)-6-fluoroindoline,

(2) 1-(piperidin-4-yl)-6-bromoindoline,

(3) 1-(piperidin-4-yl)-6-nitroindoline,

(4) 1-(piperidin-4-yl)-6-methoxyindoline,

(5) 1-(piperidin-4-yl)-6-acetamidomethylindoline,

(6) 1-(piperidin-4-yl)-6-fluoroindole,

(7) 1-(piperidin-4-yl)-6-bromoindole,

(8) 1-(piperidin-4-yl)-6-nitroindole,

(9) 1-(piperidin-4-yl)-6-methoxyindole, and

(10) 1-(piperidin-4-yl)-6-acetamidomethylindole.

Examples of the dosage forms of the compounds of the present invention include oral preparations such as powders, fine granules, granules, tablets, coated tablets and capsules, external preparations such as ointments, patches and suppositories, and injections. These preparations may be produced by the conventional methods with the use of pharmaceutical carriers commonly employed in the art.

Namely, oral preparations may be produced by blending the 1,4-substituted cyclic amine derivative or a pharmacologically acceptable salt thereof with fillers optionally together with binders, disintegrating agents, lubricating agents, coloring agents, corrigents, etc. and then processing the resultant

blends into powders, fine granules, granules, tablets, coated tablets, capsules, etc. by the conventional methods.

As the fillers, use may be made of, for example, lactose, corn starch, sucrose, glucose, mannitol, sorbitol, crystalline cellulose and silicon dioxide. As the binders, use may be made of, for example, polyvinyl alcohol, polyvinyl ether, methylcellulose, ethylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylmethylcellulose, hydroxypropylcellulose, polyvinylpyrrolidone, polypropylene glycol/polyoxyethylene block polymers and meglumine. As the disintegrating agents, use may be made of, for example, starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin, pectin and calcium carboxymethylcellulose. As the lubricating agents, use may be made of, for example, magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. As the coloring agents, use may be made of those authorized as pharmaceutical additives. As the corrigents, use may be made of, for example, cocoa powder, mentha, aromatic powder, mentha oil, borneol and powdered cinnamon bark. Needless to say, these tablets and granules may be appropriately coated with sugar, etc., if necessary.

Injections are produced by blending the 1,4-substituted cyclic amine derivative or a pharmacologically acceptable salt

thereof with pH regulating agents, resolvents, tonicity agents, etc., optionally together with dissolution aids, stabilizers, etc. and processing the resultant blends into preparations by the conventional methods.

External preparations may be produced by the conventional methods without restriction. As the bases, therefore, use can be made of various materials commonly used in drugs, quasi drugs, cosmetics, etc.

Particular examples of the base materials include animal and vegetable oils, mineral oils, ester oils, waxes, higher alcohols, fatty acids, silicone oils, surfactants, phospholipids, alcohols, polyhydric alcohols, water-soluble polymers, clay minerals and purified water. If needed, it is possible to further add pH regulating agents, antioxidants, chelating agents, antiseptics, fungicides, coloring agents, perfumes, etc., though the materials usable as the base in the external preparations of the present invention are not restricted thereto. If necessary, it is also possible to furthermore add other ingredients capable of inducing differentiation, blood flow accelerators, bactericides, antiinflammatory agents, cell activators, vitamins, amino acids, humectants, keratolytic agents, etc. The above materials may be added in such amounts as to give the concentrations thereof commonly employed in the production of

external preparations.

The clinical dose of the 1,4-substituted cyclic amine derivative of the present invention or a pharmacologically acceptable salt thereof is not restricted but varies depending on the symptoms, severity, age, complications, etc. Also, the dose thereof varies depending on the type of the salt, administration route, etc. In general, these compounds are administered to an adult in a dose of from 0.01 to 1000 mg, preferably from 0.1 to 500 mg and still preferably from 0.5 to 100 mg, per day orally, intravenously, as suppositories or percutaneously.

Next, the results of a binding test on the compounds of the present invention to serotonin 1A and serotonin 2 receptors will be given so as to illustrate the effects of the present invention. Moreover, the results of a binding test on these compounds to an $\alpha 1$ adrenalin receptor will be given so as to illustrate the safety thereof.

It is reported in, for example, the following publications that compounds with a serotonin antagonism are usable as medicament for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia:

(1) Saishin Igaku Jiten, 3rd impression of 1st edition, p. 809 "SEROTONIN", Iyaku Shuppan

(2) Stedman's Medical Dictionary, 24th edition, p. 1227 "serotonin", Williams & Wilkins

(3) Shinkei Shinpo, 37(3), 459 - 467, 1993.

(4) Iyaku Journal, 30(8), 2030 - 2068, 1994.

(5) DN & P, 5(8), 453 - 460, 1992.

(6) Annals of Neurology, 30(4), 533 - 541, 1991.

Compounds poor in the ability to bind to an α1 adrenalin receptor are medicines which would scarcely affect blood pressure in orthostatic hypotension, etc. and have a higher safety.

Effect of the Invention:

(1) Binding test on serotonin 1A, serotonin 2 and α1 adrenalin receptors

Method

(Reagent)

The following reagents were employed in this test.

1) Serotonin binoxalate (5-HT binoxalate, mfd. by Sigma Chemical Co.).

2) Methysergide maleate (mfd. by RBI).

As radioisotope-labeled compounds, use was made of the following reagents (mfd. by NEN).

3) [^{3}H] 8-Hydroxy-dipropylaminotetralin (8-OH-DPAT).

4) [^{3}H] Ketanserin hydrochloride.

5) [^{3}H] Prazosin.

These compounds and test compounds, when insoluble in water, were dissolved in ethanol and then diluted with distilled water so as to each give an ethanol concentration of 10%. Methysergide maleate was dissolved in distilled water before using.

(Animal)

Use was made of SD rats aged 6 to 8 weeks.

(Preparation of receptor source)

The rats were sacrificed by dcapitation to extirpate the cerebra. The hippocampus and cortex were separated therefrom and employed in the binding tests respectively on the serotonin 1A receptor and the serotonin 2 receptor.

The hippocampus was mixed with 50 times (on the wet weight basis) as much a 0.32 M sucrose solution while the cortex was mixed with 10 times as much the same solution. Each mixture was homogenized by using a Teflon glass homogenizer and centrifuged at 1,000 × g for 10 min. The supernatant thus obtained was further centrifuged at 20,000 × g for 20 min. The obtained precipitate was re-suspended in 50 times (based on the intial wet weight; in the case of the hippocampus) or 10 times (in the case of the cortex) as much a 50 mM Tris hydrochloride (pH 7.4) and incubated at room temperature for 30 min. After centrifuging at 20,000 × g for 20 min, the obtained precipitate was further suspended and centrifuged twice each in the same

manner. The precipitate thus obtained was suspended in 100 times (based on the initial wet weight; in the case of the hippocampus) or 20 times (in the case of the cortex) as much a 50 mM Tris hydrochloride solution (pH 7.4) to thereby give a receptor fraction. This receptor fraction was stored at -80°C until using.

(Binding test on [^{3}H] 8-hydroxy-dipropylaminotetralin)

To the receptor fraction of the hippocampus were added a test compound and 0.5 nM of [^{3}H] 8-hydroxy-dipropylamino-tetralin and the resultant mixture was incubated at room temperature for 30 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding detected in the presence of 10 μM of serotonin binoxalate was referred to as the nonspecific binding.

(Binding test on [^{3}H] ketanserin)

To the receptor fraction of the cerebral cortex were added a test compound and 0.3 nM of [^{3}H] ketanserin and the resultant mixture was incubated at 37℃ for 15 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding detected in the presence

of 1 μM of methysergide was referred to as the nonspecific binding.

IC_{50} was calculated by the probit method, while Ki was determined in accordance with the following formula:

$$Ki = IC_{50}/(1 + c/Kd)$$

wherein c represents the concentration of the radioisotope-labeled compound, and Kd represents the dissociation constant of the radioisotope-labeled compound with respect to the receptor determined by Scatchard's analysis.

(Binding test on [^{3}H] prazosin)

To the receptor fraction of the cerebral cortex were added a test compound and about 0.2 nM of [^{3}H] prazosin and the resultant mixture was incubated at room temperature for 60 min. Next, it was filtered through a glass filter with the use of a cell harvester. After washing the glass filter with 50 mM Tris hydrochloride (pH 7.4), the radioactivity of the receptor was measured with a liquid scintillation counter. The binding detected in the presence of 10 μM of phentolamine was referred to as the nonspecific binding.

The following tables show the abilities of typical examples of the compounds of the present invention to bind to the serotonin 1A and serotonin 2 receptors, wherein the number of each compound corresponds to the Example number. Also, comparison was made with cyproheptadine hydrochloride (CAS

Registry No.: 969-33-5) and cyclobenzaprine hydrochloride (CAS Registry No.: 6202-23-9) which were employed as positive controls having anti-serotonin effects.

Table 1

Ex. no.	5HT1a (nM)	5HT2 (nM)	Ex. no.	5HT1a (nM)	5HT2 (nM)
1	623.94	>200	28	46.90	8.10
3	28.70	17.40	29	—	36.50
4	6.00	24.90	30	21.90	15.70
5	10.10	8.10	31	20.80	4.10
6	4.50	17.40	32	30.20	30.20
7	34.30	12.80	33	5.70	24.30
8	13.50	26.90	34	1.90	9.10
9	3.00	11.60	35	16.60	37.60
10	8.10	6.00	36	4.50	14.90
11	5.70	27.90	37	4.60	14.80
12	8.50	16.30	38	15.00	21.80
13	24.20	>200	39	1.60	8.90
15	28.60	28.60	40	43.66	>200
16	109.32	13.85	41	19.81	5.03
17	19.01	16.36	42	35.80	5.70
18	0.13	0.12	43	4.20	37.90
19	8.80	7.00	44	4.00	43.70
20	15.20	0.22	45	15.20	6.40
21	1.90	42.70	46	1.10	4.20
22	24.00	12.20	47	206.20	92.30
23	7.40	14.60	48	15.30	35.00
24	26.50	174.20	49	54.50	29.90
25	8.30	13.10	50	31.20	52.20
26	2.90	19.50	52	2.50	5.60
27	>200	28.80	53	21.50	2.10

Table 2

Ex. no.	5HT1a (nM)	5HT2 (nM)	Ex. no.	5HT1a (nM)	5HT2 (nM)
54	7.10	10.30	81	44.30	119.00
55	41.90	17.80	82	71.20	5.30
56	20.70	1.70	84	>200	133.70
57	14.60	1.10	85	169.60	56.20
58	26.20	34.80	99	—	8.70
59	12.00	28.90	102	2.70	28.40
60	60.80	>200	103	3.90	15.80
61	5.00	12.50	104	2.40	6.00
62	6.20	7.40	105	>200	17.40
63	3.20	1.20	106	0.70	6.40
64	14.80	14.20	107	7.70	1.70
65	8.80	4.80	108	172.30	2.20
66	50.90	85.00	110	23.30	16.00
67	262.50	27.10	111	5.50	74.20
68	47.20	39.50	112	3.20	165.20
69	9.70	29.90	113	13.70	>200
70	41.90	27.60	114	5.80	23.20
71	25.40	28.20	116	0.50	14.30
72	25.90	21.10	117	0.60	10.70
73	34.90	7.20	118	0.70	10.40
75	3.60	30.30	119	0.20	45.50
76	43.20	>200	120	1.00	11.20
77	44.50	13.70	121	0.50	22.80
78	2.40	29.60	122	0.20	15.20
79	115.40	26.50	123	251.10	2.70

Table 3

Ex. no.	5HT1a (nM)	5HT2 (nM)	Ex. no.	5HT1a (nM)	5HT2 (nM)
124	1.10	45.80	152	16.40	0.27
125	0.10	4.76	153	15.48	4.24
126	1.23	129.30	154	6.52	0.0006
127	0.21	5.08	155	14.83	1.33
128	0.34	4.70	156	7.80	2.60
129	0.95	0.65	157	4.11	0.18
130	0.49	9.12	158	8.18	0.16
131	0.17	15.21	159	5.58	0.76
132	2.08	14.27	160	3.86	8.00
133	3.70	0.05	161	3.23	0.43
136	3.40	6.20	162	0.98	27.08
137	0.65	6.68	163	2.41	7.75
138	1.98	5.93	164	0.54	34.06
139	2.31	8.80	165	5.50	1.22
140	6.23	35.07	166	0.79	17.07
141	3.03	342.74	167	6.49	18.43
143	1.86	3.36	168	3.84	4.06
144	1.49	3.38	169	16.39	13.78
145	8.07	48.77	170	47.45	16.26
146	163.97	>200	171	0.39	178.00
147	1.31	0.77	172	0.12	52.43
148	9.58	0.25	173	0.06	70.07
149	7.44	0.50	174	0.24	1.85
150	13.00	0.16	175	1.49	0.35
151	8.84	0.57	176	1.67	0.05

Table 4

Ex. no.	5HT1a (nM)	5HT2 (nM)	Ex. no.	5HT1a (nM)	5HT2 (nM)
177	0.25	0.92	204	1.06	4.49
178	10.17	2.53	205	2.76	0.12
179	0.17	0.41	206	1.49	2.17
181	1029.00	9.62	207	0.81	2.69
182	4.28	2.91	208	2.33	1.05
183	1.18	3.86	209	6.98	4.72
184	15.13	3.06	210	2.50	4.93
185	14.58	4.73	211	0.53	I.21
186	14.55	3.32	212	0.82	0.36
187	65.03	5.01	213	1.03	0.18
189	7.72	2.02	214	3.50	0.90
190	0.49	0.33	215	126.40	1.00
191	29.06	0.32	216	4.70	42.90
192	1.02	2.90	218	4.50	11.70
193	6.92	2.88	219	19.60	30.90
194	4.59	>200	221	1.90	2.40
195	5.73	1.15	222	0.04	18.10
196	1.67	1.17	224	3.09	5.11
197	10.40	1.27	225	5.74	7.61
198	13.70	2.21	228	0.34	>200
199	1.98	1.19	229	2.50	>200
200	4.84	233.98	230	13.30	>200
201	7.05	>200	232	37.65	48.19
202	2.57	5.13	233	0.60	>200
203	0.55	4.61	234	1.10	3.30

Table 5

Ex. no.	5HT1a (nM)	5HT2 (nM)	Ex. no.	5HT1a (nM)	5HT2 (nM)
235	0.20	14.60	262	1.50	2.10
236	29.20	10.60	263	0.46	>200
237	30.40	>200	264	11.30	138.90
238	86.60	>200	265	25.20	34.20
240	>200	27.60	266	31.60	22.60
241	360.00	1658.30	277	22.80	3.90
242	>200	2.30	278	>200	3.90
243	>200	53.00	279	0.22	90.40
244	>200	2.50	281	35.19	11.20
245	>200	11.20	282	58.70	150.00
246	>200	60.00	283	39.50	40.90
247	>200	52.90	284	4.50	4.70
248	2.90	6.80	285	0.44	1.39
249	2.10	20.20	286	3.74	3.12
250	1.60	18.80	287	0.10	>200
251	58.50	>200	288	0.2	0.1
254	>200	176.80	291	6.9	100.6
255	>200	15.70	292	92.0	58.8
256	0.40	12.10	A	25	29
257	2.80	0.61	B	29.5	1.68
258	35.20	4.80	C	72.5	0.4
259	0.60	5.90	A: Cyclobenzaprine		
260	1.30	12.90	B: Cyproheptadine		
261	1.50	5.30	C: Co. No. 5 given in WO96/23784		

Table 5 (continuation)

Ex. no.	5HT1a (nM)	5HT2 (nM)	Ex. no.	5HT1a (nM)	5HT2 (nM)
294	1. 05	2. 86	318	1. 49	8. 3
295	0. 85	3. 64	319	0. 56	24. 5
296	0. 32	2. 73	320	0. 55	44
297	0. 98	4. 17	321	0. 14	>20
298	1. 86	21. 3	322	0. 08	30. 36
299	0. 11	2. 54	323	0. 14	>20
300	1. 73	3. 55	324	0. 1	>20
301	0. 8	21. 93	325	0. 65	10. 86
302	2. 92	60. 48	326	0. 4	>20
303	3. 6	35. 85	327	1. 04	2. 64
304	8. 37	6. 26	328	2. 06	>20
305	0. 06	3. 29	329	2. 06	2. 41
306	2. 82	3. 87	330	0. 11	>20
307	7. 02	0. 83	331	0. 11	8. 28
308	0. 73	3. 84	332	2. 24	16. 17
309	3. 85	1. 02	333	1. 08	>20
310	1. 34	2. 29	334	0. 04	>20
311	1. 08	46. 39	335	0. 22	>20
312	8. 27	0. 56	336	<0. 2	>20
313	13. 07	1. 58	337	<0. 2	>20
314	0. 72	1. 1	338	0. 07	>20
315	6. 74	1. 18	339	<0. 2	>20
316	1. 82	1. 26			
317	0. 76	>20			

Table 5 (second continuation)

Ex. no.	5HT1a (nM)	5HT2 (nM)	Ex. no.	5HT1a (nM)	5HT2 (nM)
340	3. 02	2. 84	370	>20	>20
341	2. 08	0. 67	372	>20	>20
342	0. 65	38. 15	373	0. 24	1. 77
343	1. 54	1. 64	375	1. 56	3. 37
344	1. 78	1. 64	376	0. 91	2. 1
345	4. 82	0. 29	378	14. 2	1. 54
346	13. 46	1. 49	379	9. 65	1. 25
347	2. 24	0. 65	380	2. 87	1. 56
349	0. 22	8. 12	381	1. 37	2. 02
350	1. 92	11. 44	382	7. 59	3. 31
351	0. 27	>20	383	5. 34	1. 81
352	1. 58	0. 75	384	0. 13	0. 25
353	0. 78	12. 57	385	2. 41	0. 97
354	1. 22	4. 79	386	5. 38	>20
355	0. 35	6. 87	387	63. 5	>20
356	1. 52	>20	388	2. 26	>20
357	0. 38	1. 3	389	0. 53	15. 46
358	0. 73	14. 02	390	0. 99	11. 56
359	0. 71	7. 39	391	1. 72	6. 83
360	26. 6	>20	392	0. 65	38. 15
361	0. 27	>20	393	0. 85	2. 54
362	0. 46	3. 54	394	1. 18	0. 96
363	1. 5	3. 39	397	1. 28	2. 27
364	1. 73	4. 23			
365	0. 42	3. 11			
366	0. 48	2. 05			
367	1. 63	1. 76			
368	1. 63	0. 56			
369	2. 02	2. 88			

Subsequently, the abilities of typical examples of the compounds of the present invention to bind to the α1 adrenalin receptor were evaluated by the test method described above. The following table shows the results, wherein the number of each compound corresponds to the Example number.

Also, comparison was made with Co. No. 5, as a typical example of the known compounds with a serotonin antagonism, disclosed in Table 2 of WO96/23784 and having the following chemical formula. This compound was produced in accordance with the method described in WO96/23784 (see Referential Example 1 as will be given hereinbelow).

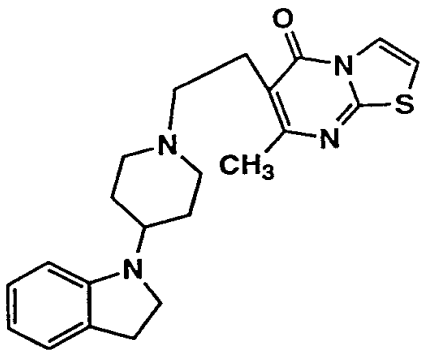


Table 6

Ex. no.	α1 (nM)	Ex. no.	α1 (nM)
9	76.5	168	72.56
11	147	182	70.07
13	188	184	188.42
19	55.5	187	>200
22	113	189	442.24
26	51.1	197	68.59
36	39	204	183.23
38	244.2	206	104.75
42	230	216	81.59
65	55.7	235	77.8
68	223.4	236	72.2
75	88.6	248	75.3
77	248.7	250	263
103	77.7	277	354.41
106	71.3	280	222
121	58.2	283	197
125	46.37	285	26.8
133	261.65	291	171.5
137	125.59	292	178.3
147	156.84		
149	304.15		
151	292.16	Cyclobenzaprine	——
162	222.63	Cyproheptadine	1900
164	638.02	Co. No. 5 given in	16.8
166	193.71	WO96/23784	

Table 6 (continuation)

Ex. no.	α1 (nM)	Ex. no.	α1 (nM)
294	80. 7	321	203
295	195. 3	322	41. 3
296	238. 5	323	86. 9
297	226. 3	324	60. 9
298	27. 9	325	47
300	224. 6	326	167
301	66. 9	327	99
302	142. 9	328	140
303	306. 9	329	149
304	141	330	338. 7
305	35. 9	331	77
306	147. 5	332	65. 9
307	51. 5	333	247. 1
308	59. 4	334	212. 2
309	122. 9	335	28. 4
310	84. 4	336	53. 7
311	85	338	21. 3
312	53. 3	339	31. 7
313	144		
314	51. 3		
316	63. 7		
317	400		
318	46. 6		
319	42. 5		
320	26. 1		

Table 6 (second continuation)

Ex. no.	α1 (nM)	Ex. no.	α1 (nM)
340	339.8	367	45.8
341	47.6	368	37.6
342	25	369	121.4
343	38.1	370	255.5
344	74.9	372	206.4
345	103.2	375	61.4
346	115.5	376	46.7
347	44.3	378	43.7
349	88.5	379	30.3
350	123.4	380	116
351	175	381	100.7
352	96.7	382	163.1
353	144.1	383	120.1
354	90.5	385	21.6
355	39.5	386	26.2
358	41.8	387	26.2
359	75.9	388	365.8
360	690	389	45
361	77.4	390	34.3
362	144	391	116.2
363	106	392	25
364	289	393	37.8
365	61.6	397	27.1
366	74.6		

Tables 1 to 6 indicate that the 1,4-substituted cyclic amine derivatives of the present invention are useful as medicaments with a serotonin antagonism and have clinical usefulness and a high safety, in particular, those for treating, ameliorating and preventing spastic paralysis or central muscle relaxants for ameliorating myotonia.

Moreover, the compounds of the present invention are superior in safety to the Co. No. 5 disclosed in WO96/23784 which is a typical example of the known compounds, since the compounds in the present invention have low abilities to bond to the α1 adrenalin receptor and scarcely affect blood pressure.

(2) Morphine induced Straub's tail phenomenon in mice

By using mice, typical examples of the compounds of the present invention were evaluated in the effect of relaxing rigidity in accordance with the method reported in Drug Dev. Res., 11:53-57, 1987.

In this test, use was made of male ddY mice aged 4 to 5 weeks (SLC, Shizuoka) which were divided into groups each comprising 8 animals. Also, use was made, as positive controls, of cyproheptadine hydrochloride, cylcobenzaprine hydrochloride, tizanidine hydrochloride (CAS Registry No.: 51322-75-9) and baclofen (CAS Registry No.: 1134-47-0). The test compounds and the positive controls were each dissolved in a 5% glucose solution for injection or suspended in a 0.5%

methylcellulose solution. Morphine hydrochloride was dissolved in physiological saline for injection.

The test compounds of the given concentrations were administered *per os* (p.o.) or intraperitoneally (i.p.) to the mice, while the media were orally administered to the control group. After 15 min of the administration of the test compounds, 12.5 mg/kg of morphine hydrochloride was subcutaneously injected into the animals. After 15, 30 and 45 min of the administration of morphine hydrochloride, the hyper-muscle tone in the tail was observed and those showing hyper-muscle tone were judged as positive in Straub's tail reaction.

The rate of those showing Straub's tail reaction in each test group was compared with that of the control group at each observation point and analyzed by the χ square calibration method to thereby determine the statistically significant ($p < 0.05$) minimal effective dose.

Now, the results of the evaluation will be shown.

Table 7

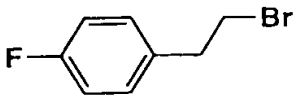
Ex. no.	i.p. (mg/kg)	p.o. (mg/kg)	Ex. no.	i.p. (mg/kg)	p.o. (mg/kg)
9	10	—	168	—	10
22	—	>10	182	—	10
34	≦10	30	184	—	3
36	1	≦3	186	—	10
42	≦10	10	189	—	10
65	—	30	197	—	10
103	≦10	>30	204	3	3
106	10	>30	206	—	10
121	—	10	235	—	>10
125	1	3	248	≦10	30
133	0.3	≦0.3	250	10	30
137	—	1	277	<1	30
147	≦0.3	≦3	285	1	1
149	1	≦3	Cyclobenzaprine	10	—
151	—	3	Cyproheptadine	3	—
162	1	>10	Tizanidine	1	1
166	3	3	Baclofen	3	10

As Table 7 clearly shows, the compounds of the present invention have excellent effects of relaxing rigidity *in vivo*.

To further illustrate the present invention in greater detail, the following Production Examples and Examples will be given. However, it is needless to say that the present invention is not restricted thereto.

[Production Example]

Production Example 1: Synthesis of 4-fluorophenethyl bromide

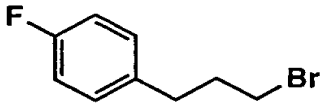


Triphenylphosphine (222 g) and N-bromosuccinimide (151 g) were added to a solution of 4-fluorophenethyl alcohol (100 g) in methylene chloride (1 l) under ice cooing, followed by stirring for 1 hr. After concentrating the resultant solution under reduced pressure, the precipitated crystals were filtered off and the filtrate was concentrated to give the title compound (133 g) as a colorless oil (yield: 92%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.14(2H, t, J=8Hz), 3.54(2H, t, J=8Hz), 6.98-7.03(2H, m), 7.15-7.18(2H, m).

Production Example 2: Synthesis of 1-bromo-3-(4-fluorophenyl)-propane



Thionyl chloride (6.8 ml) was added dropwise into ethanol (20 ml) under ice cooling, followed by stirring for 15 min. Then 3-(4-fluorophenyl)propionic acid (2.853 g) was added to the resultant solution, which was stirred at room temperature for 11 hr and concentrated under reduced pressure. The residue was diluted with ethyl acetate (500 ml), washed with a saturated aqueous solution of sodium bicarbonate and brine (a saturated aqueous solution of sodium chloride), dried over anhydrous

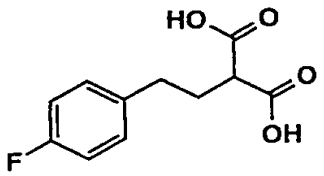
sodium sulfate, and then concentrated under reduced pressure to give a colorless oil (3.456 g). The product was dissolved in tetrahydrofuran (90 ml) and lithium aluminum hydride (0.863 g) was added to the solution under ice cooling. After stirring the mixture for 1 hr, water (0.9 ml), a 5 N aqueous solution of sodium hydroxide (0.9 ml) and further water (2.7 ml) were added thereto. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure to give a pale yellow oil (2.577 g). This oil was treated as in Example 1 to give the title compound (2.354 g) as a yellow oil (yield: 63.6%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.14(2H, tt, J=6.6, 7.0Hz), 2.76(2H, t, J=7.0Hz), 3.38(2H, t, J=6.6Hz), 6.98(2H, t, J=8.8Hz), 7.16(2H, m).

Production Example 3: Synthesis of 1-bromo-4-(4-fluorophenyl)-butane

(3-1) 3-(4-Fluorophenyl)propyl-1,1-dicarboxylic acid



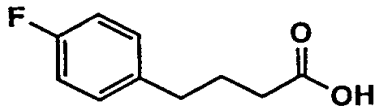
Sodium (0.7 g) was dissolved in ethanol (17.5 ml) and diethyl malonate (9.1 ml) and 4-fluorophenethyl bromide (4.1 g) were added thereto. Then the resultant mixture was heated under reflux for 2.5 hr and allowed to cool. Next, it was

diluted with ethyl acetate (500 ml), washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in ethanol (10 ml) followed by the addition of potassium hydroxide (10.2 g) dissolved in water (10 ml) thereto. The resultant mixture was stirred at 80°C for 3 hr. After allowing to cool, it was acidified with hydrochloric acid, diethyl ether was added thereto. The organic layer was separated and washed with brine, dried over anhydrous magnesium sulfate. It was then concentrated under reduced pressure to give the title compound (6.938 g) as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.25(2H, dt, J=7.6Hz), 2.70(2H, t, J=7.6Hz), 3.42(1H, t, J=7.6Hz), 6.97(2H, t, J=8.8Hz), 7.12(2H, m).

(3-2) 4-(4-Fluorophenyl)butyric acid

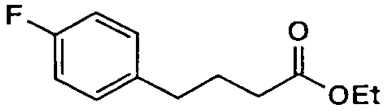


The above 3-(4-fluorophenyl)propyl-1,1-dicarboxylic acid (6.938 g) was stirred at 180°C for 40 min to give the title compound (4.877 g) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.94(2H, m), 2.37(2H, t, J=7.6Hz), 2.65(2H, t, J=7.6Hz), 6.97(2H, t, J=8.8Hz), 7.15(2H, m).

(3-3) Ethyl 4-(4-fluorophenyl)butyrate

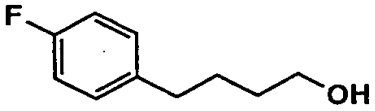


Under ice cooling, thionyl chloride (6.8 ml) was dropped into ethanol (20 ml) and the resultant solution was stirred at room temperature for 11 hr and concentrated under reduced pressure. Next, it was diluted with ethyl acetate (500 ml), washed with a saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound (7.178 g) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.34(3H, dt, J=2.0, 7.0Hz), 1.93(2H, m), 2.31(2H, dt, J=0, 7.2Hz), 2.63(2H, t, J=7.2Hz), 4.12(2H, dq, J=2.0, 7.0Hz), 6.97(2H, t, J=8.8Hz), 7.13(2H, m).

(3-4) 4-(4-Fluorophenyl)butan-1-ol



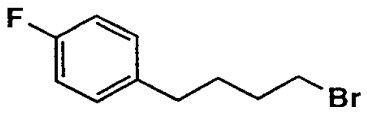
The above ethyl 4-(4-fluorophenyl)butyrate (7.178 g) was dissolved in tetrahydrofuran (120 ml) and then aluminum lithium hydride (1.55 g) was added thereto under ice cooling followed by stirring for 1 hr. After adding water (1.5 ml), 5 N aqueous solution of sodium hydroxide (1.5 ml) and further water (4.5 ml), the resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure to give the title

compound (3.890 g) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.58-1.71(4H, m), 2.61(2H, t, J=7.0Hz), 3.66(2H, dt, J=2.8, 6.4Hz), 6.96(2H, t, J=8.8Hz), 7.13(2H, m).

(3-5) 1-Bromo-4-(4-fluorophenyl)butane

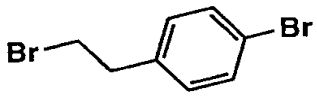


The above 4-(4-fluorophenyl)butan-1-ol (7.178 g) was treated as in the above Production Example 1 to give the title compound (4.250 g) as a yellow oil (yield: 91.9%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.75(2H, m), 1.88(2H, m), 2.62(2H, t, J=7.6Hz), 3.42(2H, t, J=7.0Hz), 6.97(2H, t, J=8.8Hz), 7.13(2H, m).

Production Example 4 Synthesis of 4-bromophenethyl bromide

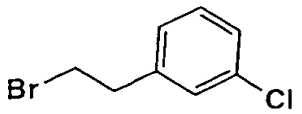


4-Bromophenethyl alcohol (1.3 ml) was treated as in Production Example 1 to give the title compound (2.345 g) as a pale yellow oil (yield: 88.8%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.12(2H, t, J=7.4Hz), 3.54(2H, t, J=7.4Hz), 7.09(2H, d, J=8.4Hz), 7.45(2H, d, J=8.4Hz).

Production Example 5 Synthesis of 3-chlorophenethyl bromide

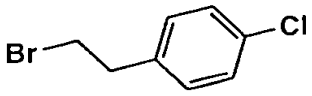


3-Chlorophenethyl alcohol (1.0 ml) was treated as in Production Example 1 to give the title compound (1.417 g) as a pale yellow oil (yield: 64.6%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.14(2H, t, J=8.6Hz), 3.56(2H, t, J=8.6Hz), 7.11(1H, m), 7.21(1H, s), 7.45(2H, m).

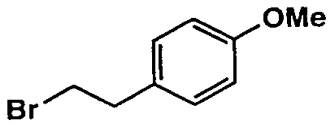
Production Example 6 Synthesis of 4-chlorophenethyl bromide



4-Chlorophenethyl alcohol (5 ml) was treated as in Production Example 1 to give the title compound (2.639 g) as a pale yellow oil (yield: 32.6%).

(no NMR)

Production Example 7 Synthesis of 4-methoxyphenethyl bromide

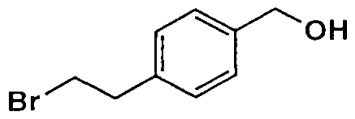


4-Methoxyphenethyl alcohol (0.61 g) was treated as in Production Example 1 to give the title compound (0.838 g) as a pale yellow oil (yield: 97.4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.10(2H, t, J=7.6Hz), 3.53(2H, t, J=7.6Hz), 3.80(3H, s), 6.86(2H, d, J=8.2Hz), 7.13(2H, d, J=8.2Hz).

Production Example 8 Synthesis of 4-(2-bromoethyl)benzyl alcohol

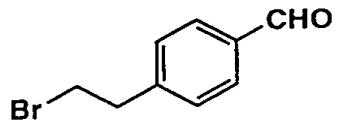


(2-Bromoethyl)benzaldehyde (1.178 g) was dissolved in ethanol (20 ml). After adding sodium borohydride (0.189 g), the resultant mixture was stirred at room temperature for 1 hr. Then it was diluted with ethyl acetate (200 ml), washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.439 g) as a pale yellow oil (yield: 40.1%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.02(1H, br-s), 3.16(2H, t, J=7.6Hz), 3.56(2H, t, J=7.6Hz), 7.20(2H, d, J=8.4Hz), 7.31(2H, d, J=8.4Hz).

Production Example 9 Synthesis of 4-(2-bromoethyl)-benzaldehyde



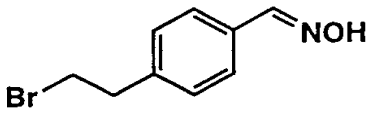
(2-Bromoethyl)benzene (2.72 ml) was dissolved in methylene chloride (20 ml). Subsequently, a 1.0 M solution (40 ml) of titanium tetrachloride in methylene chloride and dichloromethyl methyl ether (2.72 ml) were successively added dropwise thereinto while maintaining the reaction temperature

at -10°C or below. After stirring at room temperature for 6 hr, the reaction solution was poured into ice, extracted with ethyl acetate, washed successively with a saturated aqueous solution of sodium chloride, a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride again, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (5.408 g) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.26(2H, t, J=7.2Hz), 3.61(2H, t, J=7.2Hz), 7.40(2H, d, J=8.4Hz), 7.86(2H, d, J=8.4Hz), 10.01(1H, s).

Production Example 10 Synthesis of 4-(2-bromoethyl)-benzaldoxime

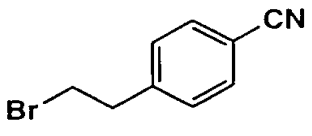


The above 4-(2-bromoethyl)benzaldehyde (2.72 g) was dissolved in ethanol (80 ml). After adding water (20 ml), hydroxylamine hydrochloride (1.53 g) and sodium acetate trihydrate (2.99 g), the resultant mixture was heated under reflux for 30 min. Then it was allowed to cool and the reaction mixture was partitioned between water and ethyl acetate (500 ml). The organic layer was washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound (5.408 g) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.18(2H, t, J=7.4Hz), 3.57(2H, t, J=7.4Hz), 7.24(2H, d, J=8.0Hz), 7.52(2H, d, J=8.0Hz), 8.13(1H, s).

Production Example 11 Synthesis of 4-cyanophenethyl bromide

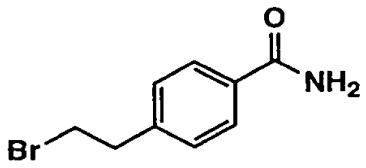


4-(2-Bromoethyl)benzaldoxime (1.0 g) was treated as in Example 20 to give the title compound (0.977 g) as a brown oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.23(2H, t, J=7.2Hz), 3.59(2H, t, J=7.2Hz), 7.34(2H, d, J=7.4Hz), 7.63(2H, d, J=7.4Hz).

Production Example 12 Synthesis of 4-carbamoylphenethyl bromide



4-Cyanophenethyl bromide (0.997 g) was dissolved in sulfuric acid (20 ml) and stirred at room temperature for 15 hr. Then it was poured into ice, diethyl ether was added thereto and the layers were separated. The organic layer was washed with a saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel

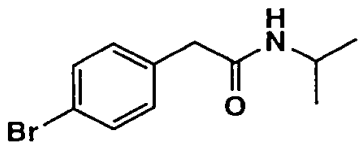
column chromatography (hexane/ethyl acetate system) to give the title compound (0.619 g) as colorless crystals (yield: 62.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.23(2H, t, J=7.3Hz), 3.59(2H, t, J=7.3Hz), 7.31(2H, d, J=8.4Hz), 7.78(2H, d, J=8.4Hz).

Production Example 13 Synthesis of N-isopropyl-4-(2-bromoethyl)phenylacetamide

(13-1) N-Isopropyl-4-bromophenylacetamide

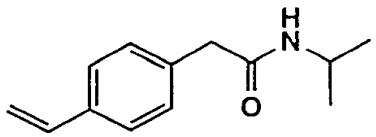


4-Bromophenylacetic acid (10 g) was dissolved in tetrahydrofuran (200 ml). After adding N,N-carbonyldiimidazole (7.54 g) thereto, the resultant mixture was stirred at room temperature for 15 min. Next, isopropylamine (3.96 ml) was further added and the resultant mixture was stirred at room temperature for 24 hr and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (500 ml) and a saturated aqueous solution of sodium bicarbonate, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give colorless crystals (11.3 g) of the title compound (yield: 94.8%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.08(6H, d, J=6.8Hz), 3.47(2H, s), 4.06(1H, m), 5.17(1H, br-s), 7.13(2H, d, J=8.8Hz), 7.47(2H, d, J=8.8Hz).

(13-2) N-Isopropyl-4-vinylphenylacetamide

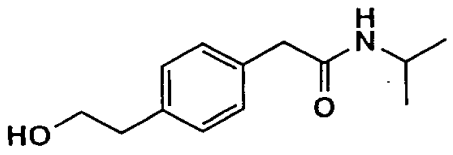


N-Isopropyl-4-bromophenylacetamide (1.0 g) and vinyltributyltin (1.4 ml) were dissolved in toluene (12 ml). After adding tetrakistriphenylphosphinepalladium (0.5 g) thereto, the resultant mixture was heated under reflux for 4 hr. Then it was allowed to cool and diluted with ethyl acetate. The resulting solid was filtered off and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give colorless crystals (0.578 g) of the title compound (yield: 72.8%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.08(6H, d, J=6.4Hz), 3.55(2H, s), 4.07(1H, m), 5.21(1H, br-s), 5.28(1H, dd, J=0.8, 10.8Hz), 5.76(1H, dd, J=0.8, 17.6Hz), 6.718(1H, dd, J=10.8, 17.6Hz), 7.21(2H, J=8.0Hz), 7.40(2H, d, J=8.8Hz).

(13-3) N-Isopropyl-4-(2-hydroxyethyl)phenylacetamide

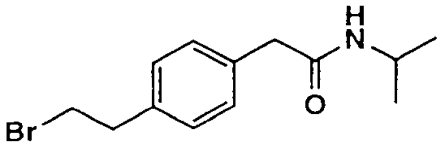


N-Isopropyl-4-vinylphenylacetamide (0.378 g) was dissolved in tetrahydrofuran (4.4 ml). Under ice cooling, a 1.0 M solution (5.6 ml) of a borane/tetrahydrofuran complex in tetrahydrofuran was added dropwise thereinto and then the resultant mixture was stirred for 2 hr. After adding a 5 N aqueous solution (3 ml) of sodium hydroxide and a 30% aqueous solution (3 ml) of hydrogen peroxide, the mixture was stirred for 10 hr. Then ethyl acetate and water were added thereto and the mixture was distributed between two liquid layers. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate-methanol system) to give colorless crystals (0.134 g) of the title compound (yield: 32.6%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.08(6H, dd, J=1.6, 6.8Hz), 2.87(2H, t, J=6.6Hz), 3.51(2H, s), 3.87(2H, t, J=6.6Hz), 4.07(1H, m), 5.26(1H, br-s), 7.19(2H, J=8.6Hz), 7.22(2H, d, J=8.6Hz).

(13-4) N-Isopropyl-4-(2-bromoethyl)phenylacetamide

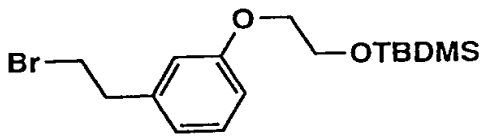


N-Isopropyl-4-(2-hydroxyethyl)phenylacetamide (0.134 g) was treated as in production Example 1 to give colorless crystals (0.029 g) of the title compound (yield: 16.9%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.08(6H, d, J=6.4Hz), 3.16(2H, t, J=7.4Hz), 3.15(2H, s), 3.57(2H, t, J=7.4Hz), 4.06(1H, m), 5.20(1H, br-s), 7.21(4H, s).

Production Example 14 Synthesis of 3-[2-(t-butyl)dimethylsilyloxyethoxyl]phenethyl bromide



[wherein TBDMS means (t-butyl)dimethylsilyl.]

3-Hydroxyphenethyl alcohol (1.5 g) and 1-bromo-2-(t-butyl)dimethylsilyloxyethane (3.4 g) were treated as in Example 35 to give a pale yellow oil. Then this product was treated as in the above Production Example 1 to give the title compound (1.996 g) as a pale yellow oil (yield: 55.4%).

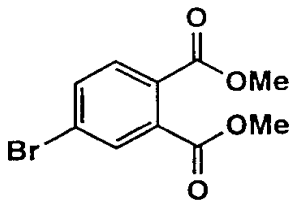
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.11(6H, s), 0.92(9H, s), 3.13(2H, t, J=7.6Hz), 3.56(2H, t, J=7.6Hz), 3.97(2H, m), 4.04(2H, m), 6.78(3H, m),

7.21(1H, m).

Production Example 15 Synthesis of 1,2-dihydroxymethyl-4-bromobenzene

(15-1) Dimethyl 4-bromophthalate

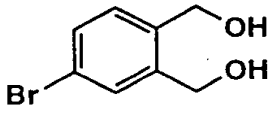


Methanol (500 ml) was added to 4-bromophthalic anhydride (50.25 g). Further, chlorosulfonic acid (1 ml) was added thereto. The resultant mixture was heated under reflux overnight and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (39.98 g) as a colorless oil (yield: 66.1%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.90(3H, s), 3.92(3H, s), 7.63(1H, d, J=8.4Hz), 7.68(1H, dd, J=2.0, 8.4Hz), 7.84(1H, d, J=2.0Hz).

(15-2) 1,2-Dihydroxymethyl-4-bromobenzene



Lithium aluminum hydride (8.77 g) was suspended in tetrahydrofuran (400 ml) and the obtained suspension was stirred under ice cooling. Into the resultant suspension was

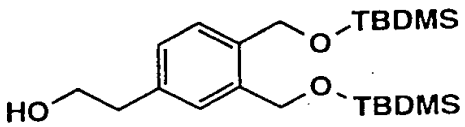
added dropwise a solution of dimethyl 4-bromophthalate (39.98 g) in tetrahydrofuran (100 ml). After stirring for additional 30 min, water (8.8 ml), a 5 N aqueous solution of sodium hydroxide (8.8 ml) and further water (26.4 ml) were successively added thereto. The resultant mixture was diluted with ethyl acetate and the insoluble matter was filtered off followed by concentration under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (13.7 g) as a colorless powder (yield: 43.1%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.18(1H, br-t), 3.27(1H, br-t), 4.63-4.65(2H, m), 7.20(1H, d, J=8.0Hz), 7.43(1H, dd, J=2.0, 8.0Hz), 7.49(1H, d, J=2.0Hz).

Production Example 16 Synthesis of 3,4-di[(t-butyl)dimethyl-silyloxymethyl]phenethyl bromide

(16-1) 3,4-Di[(t-butyl)dimethylsilyloxymethyl]phenethyl alcohol



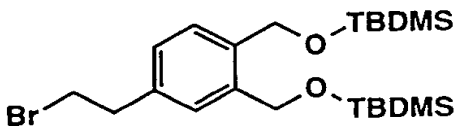
1,2-Dihydroxymethyl-4-bromobenzene (3.110 g) was treated as reported in J. Am. Chem. Soc., 6190 (1972). to give a colorless oil (6.000 g). This product was dissolved in tetrahydrofuran

(56 ml) and a solution (4.2 ml) of n-butyllithium in n-hexane and ethylene oxide (1.36 ml) were successively added thereto in a nitrogen atmosphere at -78°C followed by stirring for 3 hr. After adding water and diethyl ether to separate the layers, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (2.214 g) as a colorless oil (yield: 37.6%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.11(6H, s), 0.95(9H, s), 2.87(2H, t, J=6.4Hz), 3.85(2H, q, J=6.4Hz), 4.72(2H, s), 4.74(2H, s), 7.11(1H, dd, J=1.6, 7.6Hz), 7.29(1H, d, J=1.6Hz), 7.36(1H, d, J=7.6Hz).

(16-2) 3,4-Di[(t-butyl)dimethylsilyloxymethyl]phenethyl bromide



Pyridine (0.16 ml) was added to 3,4-dihydroxymethyl-phenethyl alcohol (0.41 g) and the resultant mixture was treated as in the above Production Example 1 to give the title compound (0.421 g) as a colorless oil (yield: 88.9%).

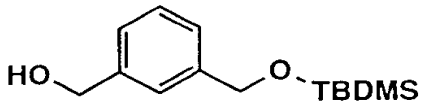
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.11(6H, s), 0.95(9H, s), 3.16(2H, t, J=7.8Hz),

3.56(2H, t, J=7.8Hz), 4.71(2H, s), 4.74(2H, s), 7.10(1H, dd, J=1.6, 7.6Hz), 7.27(1H, d, J=1.6Hz), 7.36(1H, d, J=7.6Hz).

Production Example 17 Synthesis of 3-(t-butyl)-dimethylsilyloxymethyl]phenethyl bromide

(17-1) 3-(t-Butyl)dimethylsilyloxymethylbenzyl alcohol

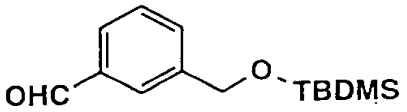


1,3-Benzenedimethanol (10 g) was dissolved in tetrahydrofuran (210 ml). Under ice cooling, sodium hydride (1.16 g) was added thereto. Next, (t-butyl)dimethyl-chlorosilane (4.36 g) dissolved in tetrahydrofuran (40ml) was added dropwise thereinto and the resultant mixture was stirred at room temperature for 3 hr. After adding water, the resultant mixture was concentrated under reduced pressure. After adding ethyl acetate (200 ml) to the residue, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (2.108 g) as a colorless oil (yield: 29.1%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.10(6H, s), 0.95(9H, s), 1.57(1H, br-s), 4.70(2H, s), 4.75(2H, s), 7.23-7.35(4H, m).

(17-2) 3-(t-Butyl)dimethylsilyloxymethylbenzaldehyde

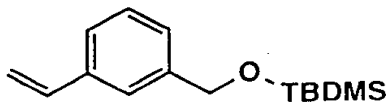


Dimethyl sulfoxide (1.43 ml) was dissolved in methylene chloride (31 ml). In a nitrogen atmosphere, oxalyl chloride (0.88 ml) was added dropwise thereinto at -78°C and the resultant mixture was stirred for 30 min. After successively adding thereto 3-(t-butyl)dimethylsilyloxymethylbenzyl alcohol (2.108 g) dissolved in methylene chloride (10 ml) and diisopropylethylamine (4.4 ml), the obtained mixture was stirred at room temperature for 1 hr. Then the reaction solution was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (2.132 g) as a colorless oil (yield: 100%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.12(6H, s), 0.95(9H, s), 4.81(2H, s), 7.50(1H, t, J=7.6Hz), 7.61(1H, d, J=7.6Hz), 7.77(1H, d, J=7.6Hz), 7.83(1H, s), 10.02(1H, s).

(17-3) 3-(t-Butyl)dimethylsilyloxymethylstyrene



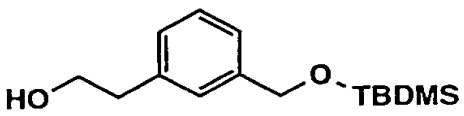
Methyltriphenylphosphonium bromide (3.16 g) was suspended in tetrahydrofuran (30 ml). Under ice cooling, potassium t-butoxide (0.99 g) was added thereto and the

resultant mixture was stirred at room temperature for 10 min. Then it was ice cooled again followed by the addition of 3-(t-butyl)dimethyl silyloxybenzaldehyde (2.132 g) dissolved in tetrahydrofuran (0.88 ml). The resultant mixture was stirred at room temperature for 5 hr. After adding water and ethyl acetate, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.930 g) as a yellow oil (yield: 93.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.10(6H, s), 0.95(9H, s), 4.74(2H, s), 5.24(1H, dd, J=1.2, 11.2Hz), 5.75(1H, dd, J=1.2, 17.6Hz), 6.72(1H, dd, J=11.2, 17.6Hz), 7.21(1H, m), 7.29(2H, m), 7.38(1H, s).

(17-4) 3-(t-Butyl)dimethylsilyloxymethylphenethyl alcohol

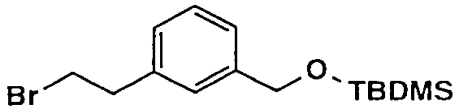


By using a 0.5 M solution of (9-boranebicyclo-[3.3.1]nonane) in tetrahydrofuran, 3-(t-butyl)dimethyl-silyloxymethylstyrene (0.5 g) was treated as reported in J. Am. Chem. Soc., 7765 (1974). to give the title compound (0.494 g) as a colorless oil (yield: 92.2%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.110(6H, s), 0.95(9H, s), 2.88(2H, t, J=6.4Hz), 3.87(2H, q, J=6.4Hz), 4.73(2H, s), 7.09-7.34(4H, m).

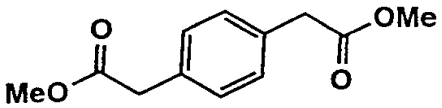
(17-5) 3-(t-Butyl)dimethylsilyloxymethylphenethyl bromide



3-(t-Butyl)dimethylsilyloxymethylphenethyl alcohol (0.494 g) was treated as in the above Production Example 1 to give the title compound (0.390 g) as a colorless oil (yield: 63.7%).

Production Example 18 Synthesis of 4-[2-(t-butyl)-dimethylsilyloxyethyl]phenethyl bromide

(18-1) Dimethyl 1,4-phenylenediacetate

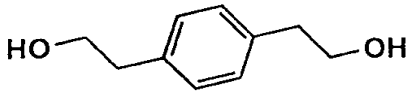


Under ice cooling, thionyl chloride (6.6 ml) was added dropwise into methanol (26 ml) and the resultant mixture was stirred for 15 min. Next, 1,4-phenylenediacetic acid (5.0 g) was added thereto and the resultant mixture was stirred at room temperature for 35 hr and then concentrated under reduced pressure. Then it was diluted with ethyl acetate (500 ml), washed with a saturated aqueous solution of sodium bicarbonate and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the title compound as colorless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.61(4H, s), 3.69(6H, s), 7.25(4H, d, J=6.4Hz).

(18-2) 1,4-Benzenediethanol

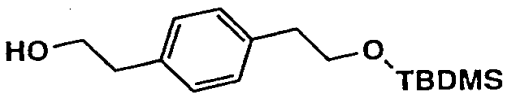


All the dimethyl 1,4-phenylenediacetate synthesized in Production Example 18-1 was dissolved in tetrahydrofuran (100 ml). Under ice cooling, lithium aluminum hydride (2.44 g) was added thereto and the resultant mixture was stirred at room temperature for 3 hr. Then it was ice cooled and water (2.5 ml), a 5 N aqueous solution of sodium hydroxide (2.5 ml) and further water (7.5 ml) were added thereto. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure to give the title compound (4.555 g) as colorless crystals.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.40(2H, t, J=6.0Hz), 2.85(4H, t, J=6.4Hz), 3.86(4H, q, J=6.4Hz), 7.19(4H, s).

(18-3) 4-[2-(t-Butyl)dimethylsilyloxyethyl]phenethyl alcohol

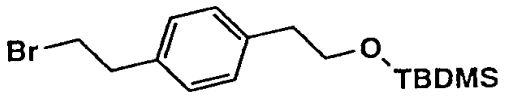


1,4-Benzenediethanol (4.555 g) was treated as in the above Production Example 17-1 to give the title compound (0.869 g) as a colorless oil (yield: 30.1%).

^{1}H-NMR (400 MHz, $CDCl_3$):

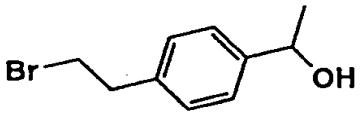
δ(ppm) -0.01(6H, s), 0.91(9H, s), 2.80(2H, t, J=7.2Hz), 2.84(2H, t, J=6.4Hz), 3.79(2H, t, J=7.2Hz), 3.84(2H, q, J=6.4Hz), 7.15(4H, s).

(18-4) 4-[2-(t-Butyl)dimethylsilyloxyethyl]phenethyl bromide



4-[2-(t-Butyl)dimethylsilyloxyethyl]phenethyl alcohol (0.869 g) was treated as in the above Production Example 1 to give the title compound (0.700 g) as a colorless oil (yield: 65.8%).

Production Example 19 Synthesis of 4-(1-hydroxyethyl)-phenethyl bromide



4-(2-Bromoethyl)benzaldehyde (3.245 g) was dissolved in tetrahydrofuran (60 ml). Under ice cooling, a 3 M solution (4.9 ml) of methylmagnesium bromide in diethyl ether was added dropwise thereinto and the resultant mixture was stirred for 1.5 hr. After adding water and ethyl acetate, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was then purified by silica gel column

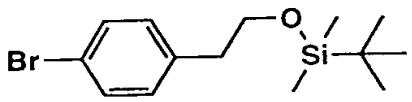
chromatography (hexane/ethyl acetate system) to give the title compound (2.745 g) as a brown oil (yield: 83.8%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.49(3H, d, J=6.4Hz), 1.81(1H, br-s), 3.16(2H, t, J=7.6Hz), 3.57(2H, t, J=7.6Hz), 4.89(1H, q, J=6.4Hz), 7.20(2H, d), 7.33(2H, d).

Production Example 20 Synthesis of 4-methanesulfonyl-phenethyl bromide

(20-1) 4-(2-t-Butyldimethylsiloxyethyl)-1-bromobenzene

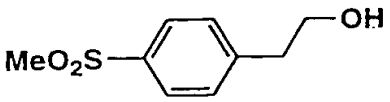


A solution of 4-bromophenethyl alcohol (10 g), imidazole (4.0 g) and (t-butyl)dimethylsilyl chloride (9.0 g) in dimethylformamide (50 ml) was stirred at room temperature for 3 hr. Then the reaction solution was concentrated under reduced pressure. After adding water and ethyl acetate, the layers were separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. After evaporating the solvent, the residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (13.9 g) as a colorless oil (yield: 88%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) -0.02(6H, s), 0.89(9H, s), 2.79(2H, t, J=7Hz), 3.80(2H, t, J=7Hz), 7.10(2H, d, J=8Hz), 7.42(2H, d, J=8Hz).

(20-2) 4-Methanesulfonylphenethyl alcohol



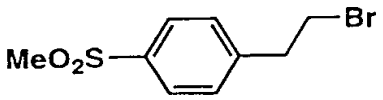
A 2.5 M solution (7.6 ml) of (n-butyllithium) in hexane was added dropwise at -78°C into a solution of 4-[2-(t-butyl)-dimethylsiloxyethyl]-1-bromobenzene (5.0 g) in tetrahydrofuran (50 ml) over 10 min. After 10 min, a saturated solution of sulfur dioxide in tetrahydrofuran (200 ml) was added thereto and the resultant mixture was warmed to room temperature. After concentrating the reaction solution under reduced pressure, dimethylformamide (100 ml) and methyl iodide (2.7 g) were added to the obtained residue followed by stirring at 50°C for 6 hr. After concentrating under reduced pressure, a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue was added tetrahydrofuran and tetrabutylammonium fluoride followed by stirring at 0°C for 2 hr. After adding water and ethyl acetate to the reaction solution, the layers were separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (methylene chloride/ethanol system) to give the title compound (1.9 g) as

a colorless oil (yield: 60%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.45(1H, t, J=7Hz), 2.85(2H, t, J=7Hz), 3.04(3H, s), 3.92(2H, q, J=7Hz), 7.44(2H, d, J=8Hz), 7.89(2H, d, J=8Hz).

(20-3) 4-Methanesulfonylphenethyl bromide

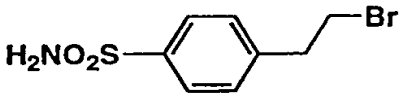


4-Methanesulfonylphenethyl alcohol (1.9 g) was treated as in the above Production Example 1 to give the title compound (1.9 g) as a colorless oil (yield: 76%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.05(3H, s), 3.27(2H, t, J=7Hz), 3.61(2H, t, J=7Hz), 7.43(2H, d, J=8Hz), 7.90(2H, d, J=8Hz).

Production Example 21 Synthesis of 4-sulfamoylphenethyl bromide



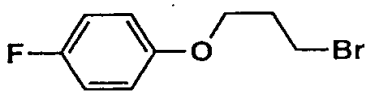
Under ice cooling, phenethyl bromide (5.0 g) was added dropwise into chlorosulfonic acid (15 ml) followed by stirring for 1 hr. The reaction solution was diluted with ice water and ethyl acetate and the layers were separated. Then the organic layer was washed with brine. Then aqueous ammonia (10 ml) was added thereto and the resultant mixture was stirred for 1 hr. The organic layer was washed with brine, dried over anhydrous

magnesium sulfate and concentrated under reduced pressure. The crystalline precipitates were washed with isopropyl ether and air-dried to give the title compound (1.4 g) as white crystals (yield: 22%).

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 3.20(2H, t, J=7Hz), 3.31(2H, br-s), 3.77(2H, t, J=7Hz), 7.48(2H, d, J=8Hz), 7.74(2H, d, J=8Hz).

Production Example 22 Synthesis of 1-bromo-3-(4-fluoro-phenoxy)propane



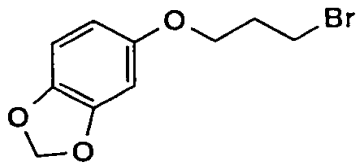
A mixture of 4-fluorophenol (11 g), 1,3-dibromopropane (61 g), sodium hydroxide (8.0 g), tetra-n-butylammonium bromide (6.0 g), methylene chloride (200 ml) and water (200 ml) was vigorously stirred at room temperature overnight. After separating the organic layer, it was washed with brine and dried over anhydrous magnesium sulfate. The residue was then purified by silica gel column chromatography (hexane/isopropyl ether system) to give the title compound (16.5 g) as a colorless oil (yield: 71%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.24-2.36(2H, m), 3.60(2H, t, J=7Hz), 4.08(2H, t, J=7Hz), 6.80-6.89(2H, m), 6.93-7.00(2H, m).

Production Example 23 Synthesis of 3-bromopropoxy-1,2-

methylenedioxybenzene

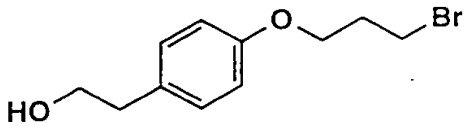


3,4-Methylenedioxyphenol (4.144 g) was dissolved in N,N-dimethylformamide (40 ml). Under ice cooling, 60% sodium hydride (1.2 g) was added thereto and the resultant mixture was stirred. After 1 hr, 1,3-dibromopropane (9.1 ml) was added thereto followed by stirring at room temperature overnight. The reaction mixture was diluted with ethyl acetate and water and the layers were separated. Then the organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane system) to give the title compound (1.341 g) as a colorless solid (yield: 17%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.25-2.32(2H, m), 3.59(2H, t, J=6.4Hz), 4.03(2H, t, J=5.8Hz), 5.92(2H, s), 6.33(1H, dd, J=8.8Hz, 2.4Hz), 6.49(1H, d, J=2.4Hz), 6.71(1H, d, J=8.8Hz).

Production Example 24 Synthesis of 4-(3-bromopropoxy)-phenethyl alcohol

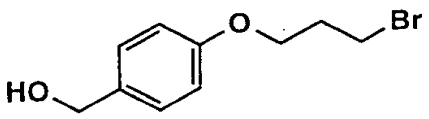


4-Hydroxyphenethyl alcohol (4.145 g), 1,3-dibromopropane (9.1 ml) and tetrabutylammonium bromide (967 mg) were added to methylene chloride (100 ml) and a solution of sodium hydroxide (2.4 g) in water (100 ml) and the resultant mixture was vigorously stirred at room temperature overnight. The methylene chloride layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane system) to give the title compound (1.005 g) as a colorless solid (yield: 13%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.31(2H, qui, J=6Hz), 2.81(2H, t, J=6.4Hz), 3.60(2H, t, J=6.4Hz), 3.83(2H, t, J=6.4Hz), 4.09(2H, t, J=6Hz), 6.86(2H, d, J=8.6Hz), 7.08(2H, d, J=8.6Hz).

Production Example 25 Synthesis of 4-(3-bromopropoxy)benzyl alcohol



4-Hydroxybenzyl alcohol (3.724 g) was treated as in the above Production Example 24 to give the title compound (314 mg)

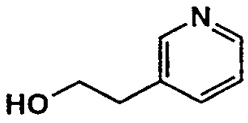
as a pale yellow solid (yield: 4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.31(2H, qui, J=6.3Hz), 3.30(2H, t, J=6.3Hz), 4.10(2H, t, J=6.3Hz), 4.60(2H, d, J=5.8Hz), 6.90(2H, d, J=8.9Hz), 7.30(2H, d, J=8.9Hz).

Production Example 26 Synthesis of 3-(2-bromoethyl)pyridine

(26-1) 3-Pyridylethanol

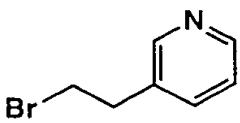


Ethyl 3-pyridylacetate (2.0 ml) was dissolved in tetrahydrofuran (66 ml). Under ice cooling, lithium aluminum hydride (0.5 g) was added thereto followed by stirring for 30 min. After adding water (0.5 ml), a 5 N aqueous solution of sodium hydroxide (0.5 ml) and further water (1.5 ml), the resulting precipitate was filtered off and washed with ethyl acetate. The filtrate was concentrated under reduced pressure to give the title compound (1.636 g) as a pale yellow oil (1.636 g) (yield: quantitative).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.84(2H, t, J=6.4Hz), 3.85(2H, t, J=6.4Hz), 7.20(1H, m), 7.57(1H, m), 8.36(2H, m).

(26-2) 3-(2-Bromoethyl)pyridine



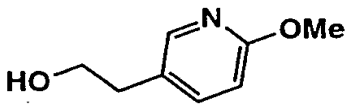
3-Pyridylethanol (0.4 g) was treated as in the above Production Example 1. The liquid reaction mixture was reverse extracted with 1 N hydrochloric acid and then basified with an aqueous solution of sodium hydroxide. Next, it was extracted with chloroform, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (0.481 g) as a brown oil (yield: 79.5%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.18(2H, t, J=7.2Hz), 3.58(2H, t, J=7.2Hz), 7.47(1H, m), 7.55(1H, dt, J=1.6, 7.2Hz), 7.67(1H, ddd, J=1.6, 7.2, 10.8Hz), 8.51(1H, m).

Production Example 27 Synthesis of 1-bromo-2-(2-methoxypyridin-5-yl)ethane

(27-1) 2-(2-Methoxypyridin-5-yl)ethanol



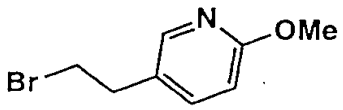
5-Bromo-2-methoxypyridine (2.628 g) synthesized as reported in Tetrahedron, 1373 (1985). was dissolved in diethyl ether (40 ml) and then treated as in the above Production Example 16-1 to give the title compound (1.342 g) as a pale yellow oil (yield: 62.7%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.79(2H, t, J=6.4Hz), 3.82(2H, br-t), 3.91(3H, s), 6.71(1H, d, J=8.4Hz), 7.46(1H, dd, J=2.4, 8.4Hz), 8.01(1H, d,

J=2.4Hz).

(27-2) 1-Bromo-2-(2-methoxypyridin-5-yl)ethane



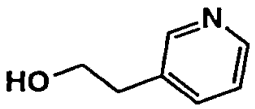
2-(2-Methoxypyridin-5-yl)ethanol (1.342 g) was treated as in the above Production Example 1. After the completion of the reaction, reverse extraction method was effected to give the title compound (1.221 g) as a brown oil (yield: 64.5%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.09(2H, t, J=7.4Hz), 3.52(2H, t, J=7.4Hz), 3.93(3H, s), 6.71(1H, d, J=8.4Hz), 7.44(1H, dd, J=2.4, 8.4Hz), 8.02(1H, d, J=2.4Hz).

Production Example 28 Synthesis of 1-bromo-2-(2-cyanopyridin-5-yl)ethane

(28-1) 2-(3-Pyridyl)ethanol



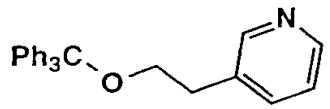
3-Pyridylacetic acid hydrochloride (25 g) was treated successively as in the above Production Examples 3-3 and 3-4 to give the title compound (16.938 g) as a yellow oil (yield: 95.5%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.86(2H, t, J=6.8Hz), 3.88(2H, t, J=6.8Hz), 7.22(1H, dd, J=4.8, 7.6Hz), 7.527(1H, d, J=7.6Hz), 8.42(1H, dd, J=2.0,

4.8Hz), 8.44(1H, d, J=2.0Hz).

(28-2) 2-(3-Pyridyl)-1-triphenylmethyloxyethane

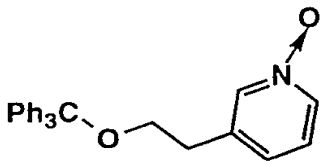


2-(3-Pyridyl)ethanol (5.0 g) was treated as reported in Tetrahedron Lett., 579 (1986). to give the title compound (10.096 g) as a yellow oil (yield: 68.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.86(2H, t, J=6.4Hz), 3.32(2H, t, J=6.4Hz), 7.08-7.38(16H, m), 7.53(1H, d, J=8.0Hz), 8.46(2H, m).

(28-3) 3-(2-Triphenylmethyloxyethyl)pyridin N-oxide

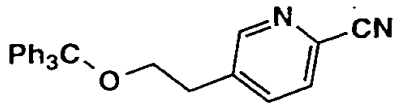


2-(3-Pyridyl)-1-triphenylmethyloxyethane (10.096 g) was treated as reported in Tetrahedron Lett., 1475 (1986). to give the title compound (11.201 g) as a yellow oil (yield: quantitative).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.86(2H, t, J=6.4Hz), 3.32(2H, t, J=6.4Hz), 7.08-7.38(16H, m), 7.53(1H, d, J=8.0Hz), 8.46(2H, m).

(28-4) 2-(2-Cyanopyridin-5-yl)-1-triphenylmethyloxyethane

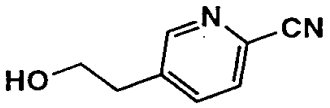


2-Cyano-5-(2-triphenylmethyloxyethyl)pyridine N-oxide (8.0 g) and trimethylsilyl cyanide (11.2 ml) were treated as reported in Synthesis, 314 (1983). to give the title compound (2.831 g) as a pale yellow oil (yield: 30.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.91(2H, t, J=6.0Hz), 3.38(2H, t, J=6.0Hz), 7.20-7.35(16H, m), 7.60(2H, m), 8.55(1H, s).

(28-5) 2-(2-Cyanopyridin-5-yl)ethanol

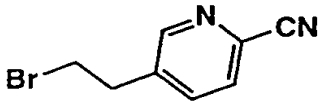


2-(2-Cyanopyridin-5-yl)-1-triphenylmethyloxyethane (2.631 g) and formic acid (38.0 ml) were treated as reported in Tetrahedron Lett., 579 (1986). to give the title compound (0.455 g) as colorless crystals (yield: 45.7%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.95(2H, t, J=5.8Hz), 3.94(2H, t, J=5.8Hz), 7.64(1H, d, J=8.0Hz), 7.75(1H, dd, J=2.0, 8.0Hz), 8.61(1H, d, J=2.0Hz).

(28-6) 1-Bromo-2-(2-cyanopyridin-5-yl)ethane



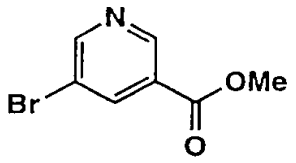
2-(2-Cyanopyridin-5-yl)ethanol (0.423 g) was treated as in the above Production Example 1 to give the title compound (0.406 g) as colorless crystals (yield: 67.3%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.30(2H, t, J=6.8Hz), 3.94(2H, t, J=6.8Hz), 7.71(1H, d, J=8.0Hz), 7.78(1H, dd, J=2.4, 8.0Hz), 8.62(1H, d, J=2.4Hz).

Production Example 29 Synthesis of 5-(2-bromoethyl)-3-(t-butyl)dimethylsilyloxymethylpyridine

(29-1) Methyl 5-bromonicotinate

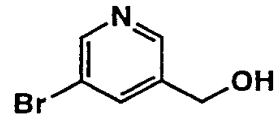


5-Bromonicotinic acid (10 g) and methanol were treated as in the above Production Example 3-3 to give the title compound (10.052 g) as colorless crystals (yield: 94.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.97(3H, s), 8.44(1H, dd, J=1.6, 2.4Hz), 8.85(1H, d, J=2.4Hz), 9.13(1H, d, J=1.6Hz).

(29-2) 5-Bromo-3-hydroxymethylpyridine

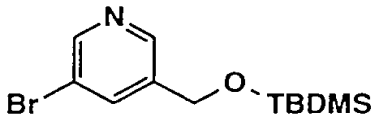


Methyl 5-bromonicotinate (5.0 g) and methanol were treated as in the above Production Example 3-4 to give the title compound (3.410 g) as a yellow oil (yield: 78.4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.50(1H, m), 3.97(2H, s), 7.90(1H, s), 8.48(1H, s), 8.58(1H, s).

(29-3) 5-Bromo-3-(t-butyldimethylsilyloxymethyl)pyridine

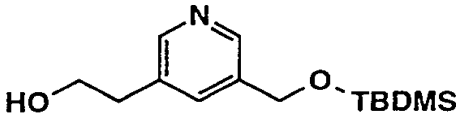


5-Bromo-3-hydroxymethylpyridine (3.41 g), imidazole (13.33 g), t-butyldimethylchlorosilane (13.57 g) and N,N-dimethylformamide (63 ml) were treated as reported in J. Am. Chem. Soc., 6190 (1972) to give the title compound (5.605 g) as a yellow oil (yield: quantitative).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.12(6H, s), 0.95(9H, s), 4.74(2H, s), 7.81(1H, s), 8.47(1H, s), 8.56(1H, s).

(29-4) 5-(2-Hydroxyethyl)-3-(t-butyl)dimethylsilyloxy-methylpyridine

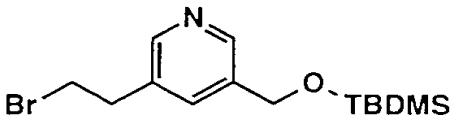


5-Bromo-3-(t-butyl)dimethylsilyloxymethylpyridine (3.41 g) and diethyl ether employed as a solvent were treated as in the above Production Example 16-1 to give the title compound (0.827 g) as a brown oil (yield: 26.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.12(6H, s), 0.95(9H, s), 1.61(1H, m), 2.88(2H, t, J=6.4Hz), 3.89(2H, q, J=6.4Hz), 4.75(2H, s), 7.54(1H, s), 8.38(1H, s), 8.43(1H, s).

(29-5) 5-(2-Bromoethyl)-3-(t-butyl)dimethylsilyloxy-methylpyridine

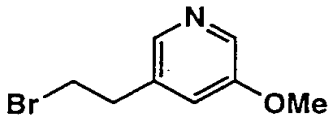


5-(2-Hydroxyethyl)-3-(t-butyl)dimethylsilyloxymethylpyridine (0.4 g) was treated as in the above Production Example 1 to give the title compound (0.248 g) as a yellow oil (yield: 50.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.12(6H, s), 0.95(9H, s), 3.18(2H, t, J=7.2Hz), 3.57(2H, t, J=7.2Hz), 4.76(2H, s), 7.53(1H, s), 8.38(1H, d, J=2.0Hz), 8.46(1H, d, J=2.0Hz).

Production Example 30 Synthesis of 5-(2-bromoethyl)-3-methoxypyridine



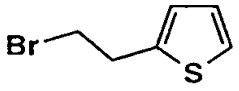
Methoxymethyltriphenylphosphonium chloride (3.0 g) was suspended in tetrahydrofuran (10 ml). Under ice cooling, potassium t-butoxide (0.98 g) was added thereto followed by stirring for 15 min. Next, 5-methoxy-3-pyridinecarboxyaldehyde (0.4 g) synthesized as reported in Heterocycles, 2159 (1987). and dissolved in tetrahydrofuran (5 ml) was added thereto and the resultant mixture was stirred at room temperature for 2 hr. After adding water and ethyl acetate thereto, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and

concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give a yellow oil (0.364 g). This product was dissolved in 1 N hydrochloric acid (44 ml) and stirred at 60°C for 3 hr. After allowing to cool, the reaction solution was basified with an aqueous solution of sodium hydroxide, extracted with chloroform, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a yellow oil (0.220 g). This product was dissolved in ethanol (7.2 ml) and sodium tetrahydroborate (0.054 g) was added thereto under ice cooling. After stirring at room temperature for 30 min, the resultant mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give a pale yellow oil (0.188 g). This product was treated as in the above Production Example 1 to give the title compound (0.181 g) as a brown oil (yield: 28.4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.16(2H, t, J=6.4Hz), 3.57(2H, t, J=6.4Hz), 3.88(3H, s), 7.08(1H, s), 8.10(1H, s), 8.21(1H, s).

Production Example 31 Synthesis of 2-(2-bromoethyl)thiophene



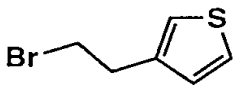
2-Thienylethanol (0.44 ml) was treated as in the above

Production Example 1 to give the title compound (0.490 g) as a colorless oil (yield: 64.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.38(2H, t, J=7.6Hz), 3.58(2H, t, J=7.6Hz), 6.89(1H, d, J=1.2Hz), 6.96(1H, d, J=4.2Hz), 7.19(1H, dd, J=1.2, 4.2Hz).

Production Example 32 Synthesis of 3-(2-bromoethyl)thiophene



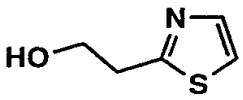
3-Thienylethanol (0.45 ml) was treated as in the above Production Example 1 to give the title compound (0.389 g) as a pale yellow oil (yield: 59.9%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.21(2H, t, J=7.6Hz), 3.57(2H, t, J=7.6Hz), 6.98(1H, d, J=4.8Hz), 7.09(1H, s), 7.29(1H, d, J=4.8Hz).

Production Example 33 Synthesis of 2-(2-bromoethyl)thiazole

(33-1) 2-(2-Hydroxyethyl)thiazole

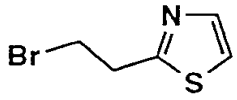


Thiazole (5.0 g) was dissolved in diethyl ether (150 ml) and treated as in the above Production Example 16-1 to give the title compound (1.173 g) as a brown oil (yield: 15.5%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.24(2H, t, J=6.0Hz), 4.02(2H, m), 7.23(1H, d, J=3.4Hz), 7.69(1H, d, J=3.4Hz).

(33-2) 2-(2-Bromoethyl)thiazole



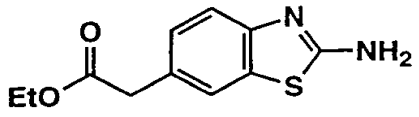
2-(2-Hydroxyethyl)thiazole (1.173 g) was treated as in the above Production Example 1 to give the title compound (0.362 g) as a pale yellow oil (yield: 24.9%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.57(2H, t, J=7.2Hz), 3.75(2H, t, J=7.2Hz), 7.26(1H, d, J=3.4Hz), 7.74(1H, d, J=3.4Hz).

Production Example 34 Synthesis of 6-(2-bromoethyl)benzothiazole

(34-1) 2-Amino-6-ethoxycarbonylmethylbenzothiazole



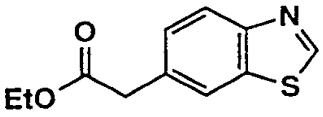
Ethyl 4-aminophenylacetate (18 g) was dissolved in acetic acid (120 ml) and ethyl thiocyanate (29.3 g) was added thereto. Under ice cooling, bromine (6.2 ml) was added dropwise thereinto over 45 minutes while maintaining the reaction temperature at about 10°C. After the completion of the addition, the resultant mixture was stirred at room temperature for 1.5 hr and then at 80°C for about 2 hr until the reaction was completed. Then the reaction solution was poured into ice water, basified with an 8 N aqueous solution of sodium hydroxide, extracted with chloroform, washed with water, dried over anhydrous magnesium

sulfate and then concentrated under reduced pressure to give the title compound (22.23 g) as orange crystals (yield: 93.66%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.26(3H, t, J=7.2Hz), 3.65(2H, s), 4.16(2H, q, J=7.2Hz), 5.31(2H, br-s), 7.22(1H, dd, J=2.0, 8.4Hz), 7.48(1H, d, J=8.4Hz), 7.53(1H, d, J=2.0Hz).

(34-2) Ethyl (6-benzothiazolyl)acetate

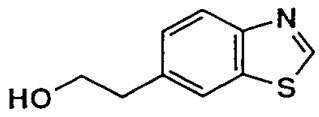


2-Amino-6-ethoxycarbonylmethylbenzothiazole (2.0 g) was dissolved in N,N-dimethylformamide (17 ml) and isoamyl nitrite (2.3 ml) was added dropwise into the solution at 65°C. Then the resultant mixture was stirred as such for 15 min. After allowing to cool, the reaction solution was poured into ice water, extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.341 g) as an orange oil (yield: 71.6%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.26(3H, t, J=7.2Hz), 3.77(2H, s), 4.18(2H, q, J=7.2Hz), 7.45(1H, d, J=8.4Hz), 7.90(1H, s), 8.09(1H, d, J=8.4Hz), 8.97(1H, s).

(34-3) 6-(2-Hydroxyethyl)benzothiazole

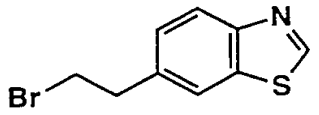


Ethyl (6-benzothiazolyl)acetate (0.22 g) was treated as in the above Production Example 18-2 to give the title compound (0.130 g) as a brown oil (yield: 72.5%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.14(1H, m), 3.01(2H, t, J=6.4Hz), 3.93(2H, t, J=6.4Hz), 7.36(1H, dd, J=1.6, 8.4Hz), 7.81(1H, d, J=1.6Hz), 8.02(1H, d, J=8.4Hz), 8.97(1H, s).

(34-4) 6-(2-Bromoethyl)benzothiazole

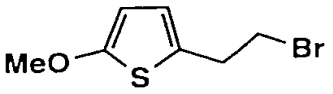


6-(2-Hydroxyethyl)benzothiazole (0.130 g) was treated as in the above Production Example 1. Then the reaction solution was directly purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.080 g) as a yellow oil (yield: 45.5%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.32(2H, t, J=7.6Hz), 3.64(2H, t, J=7.6Hz), 7.37(1H, dd, J=1.6, 8.4Hz), 7.82(1H, d, J=1.6Hz), 8.09(1H, d, J=8.4Hz), 8.97(1H, s).

Production Example 35 Synthesis of (5-methoxy-2-thienyl)ethyl bromide



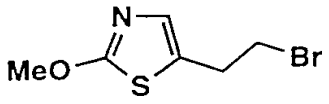
A 2.5 M solution (23 ml) of n-butyllithium in hexane was added dropwise at -78°C into a solution of 2-methoxythiophene (5.0 g) in ether (50 ml). Then the resultant mixture was warmed to room temperature and stirred. After 10 min, ethylene oxide (2.5 g) was added dropwise thereinto at -78°C and then the resultant mixture was warmed to room temperature and stirred for 1 hr. After adding a saturated aqueous solution of ammonium chloride and ethyl acetate, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and purified by silica gel column chromatography (hexane/ethyl acetate system). Then it was diluted with methylene chloride (50 ml) and triphenylphosphine (4.0 g) and N-bromosuccinimide (2.7 g) were added thereto under ice cooling followed by stirring overnight. After concentrating under reduced pressure, the resulting crystalline precipitates were filtered off and the filtrate was concentrated to give the title compound (1.7 g) as a brown oil (yield: 18%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.19(2H, t, J=7Hz), 3.51(2H, t, J=7Hz), 3.85(3H, s), 6.01(1H, d, J=4Hz), 6.47(1H, d, J=4Hz).

Production Example 36 Synthesis of (2-methoxy-5-

thiazolyl)ethyl bromide



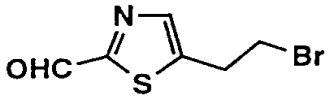
2-Methoxythiazole (3.9 g) was treated as in the above Production Example 35 to give the title compound (1.4 g) as a brown oil (yield: 19%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.20(2H, t, J=7Hz), 3.51(2H, t, J=7Hz), 4.03(3H, s), 6.89(1H, s).

Production Example 37 Synthesis of (2-cyano-5-thiazolyl)-ethyl bromide

(37-1) (2-Formyl-5-thiazolyl)ethyl bromide



A solution of 2-formylthiazole (5.0 g), trimethylene glycol (6.7 g) and p-toluenesulfonic acid (0.5 g) in toluene (100 ml) was heated under reflux overnight. Then a saturated aqueous solution of sodium bicarbonate was added to the reaction solution and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was diluted with ether (200 ml). Then a 2.5 M solution (23 ml) of n-butyllithium in hexane was dropped at -78°C thereinto followed by warming to room temperature and stirring. After 10 min,

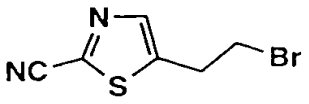
ethylene oxide (2.5 g) was added dropwise thereinto at -78°C and then the resultant mixture was warmed to room temperature and stirred for 1 hr. After adding a saturated aqueous solution of ammonium chloride and ethyl acetate thereto, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and purified by silica gel column chromatography (hexane/ethyl acetate system). Then it was diluted with methylene chloride (50 ml) and triphenylphosphine (3.9 g) and N-bromosuccinimide (2.7 g) were added thereto under ice cooling followed by stirring overnight. After concentrating under reduced pressure, the resulting crystalline precipitates were filtered off and the filtrate was concentrated. The residue was diluted with tetrahydrofuran (20 ml) and 2 N hydrochloric acid (30 ml) was added thereto. After heating under reflux for 1 day, the reaction solution was basified by adding an aqueous solution of sodium hydroxide. After adding ethyl acetate thereto, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was then purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (2.5 g) as a brown oil (yield: 26%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.40(2H, t, J=7Hz), 3.78(2H, t, J=7Hz), 7.94(1H,

s), 9.93(1H, s).

(37-2) (2-Cyano-5-thiazolyl)ethyl bromide



A suspension of the above (2-formyl-5-thiazolyl)ethyl bromide (2.5 g), hydroxylammonium chloride (0.79 g) and anhydrous sodium acetate (1.87 g) in ethanol (50 ml) was stirred at room temperature for a day. The reaction solution was diluted with ethyl acetate and water and then basified with an 8 N aqueous solution of sodium hydroxide followed by separation of an organic layer. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After evaporating the solvent, the residue was diluted with methylene chloride (50 ml) followed by the addition of triethylamine (2.3 g). Then trifluoromethanesulfonic anhydride (3.2 g) was added dropwise thereinto at -78°C and the resultant mixture was heated to room temperature. After adding a saturated aqueous solution of sodium bicarbonate and chloroform thereto, the layers were separated and the organic layer was dried over anhydrous magnesium sulfate and purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.2 g) as a brown oil (yield: 8.1%).

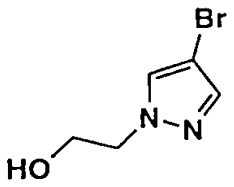
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.40(2H, t, J=7Hz), 3.76(2H, t, J=7Hz), 7.87(1H,

s).

Production Example 38 Synthesis of 1-(2-bromoethyl)-4-bromopyrazole

(38-1) 1-(2-Hydroxyethyl)-4-bromopyrazole

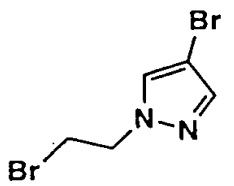


1-(2-Benzyloxyethyl)-4-bromopyrazole (1.078 g) was dissolved in ethanol (20 ml). After adding conc. hydrochloric acid (15 ml), the resultant mixture was stirred at 80°C for 10 hr. After allowing to cool, it was concentrated under reduced pressure followed by the addition of a saturated aqueous solution of sodium bicarbonate. Then the resultant mixture was extracted with ethyl acetate and the organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (525 mg) as a colorless oil (yield: 71%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.30(1H, br-s), 3.90(2H, t, J=5Hz), 4.15(2H, t, J=5Hz), 7.40(1H, s), 7.45(1H, s).

(38-2) 1-(2-Bromoethyl)-4-bromopyrazole

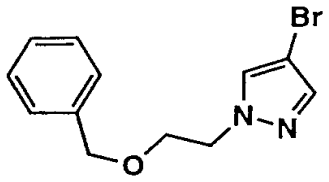


1-(2-Hydroxyethyl)-4-bromopyrazole (525 mg) was treated as in the above Production Example 1 to give the title compound (200 mg) as a colorless oil (yield: 30%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.61(2H, t, J=6.2Hz), 4.62(2H, t, J=6.2Hz), 7.50(1H, s), 7.51(1H, s).

Production Example 39 Synthesis of 1-(2-benzyloxyethyl)-4-bromopyrazole



4-Bromopyrazole (2.205 g) was dissolved in tetrahydrofuran (20 ml). Under ice cooling, 60% sodium hydride (625 mg) was added thereto followed by stirring. After 30 min, benzyl 2-bromoethyl ether (3.872 g) obtained from 2-benzyloxyethanol in the same manner as the one of Production Example 1 was added thereto and the resultant mixture was stirred at room temperature overnight. Then the reaction solution was partitioned between ethyl acetate and water and the organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to give the title compound (2.287 g) as a colorless oil (yield: 53%).

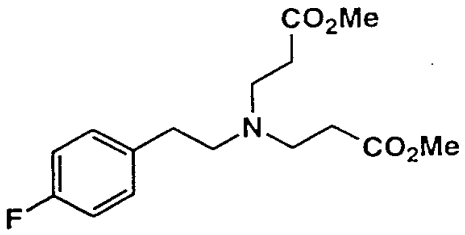
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.79(2H, t, J=5.4Hz), 4.29(2H, t, J=5.4Hz), 4.48(2H,

s), 7.22-7.48(5H, m), 7.46(1H, s), 7.52(1H, s).

Production Example 40 Synthesis of 1-[2-(4-fluorophenyl)-ethyl]-3-methyl-4-piperidone

(40-1) Bis(methylpropionyl)-4-fluorophenethylamine

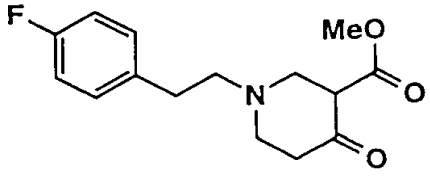


4-Fluorophenethylamine (236.87 g) was dissolved in methanol (360 ml) and ice cooled. Then methyl acrylate (360 ml) was added dropwise thereinto over 30 min followed by heating under reflux for 10 hr. After concentrating under reduced pressure, the title compound (527.04 g) was obtained as a colorless oil (yield: 99.5%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.43(4H, t, J=7.6Hz), 2.62-2.83(4H, m), 2.83(4H, t, J=7.6Hz), 3.66(6H, s), 6.95(2H, t, J=8.8Hz), 7.12(2H, dd, J=4.8, 8.8Hz).

(40-2) 1-Fluorophenethyl-3-methoxycarbonyl-4-piperidone (sodium salt)



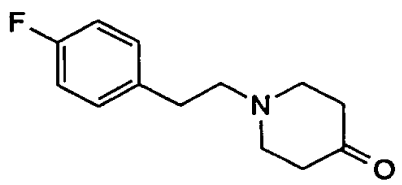
Under ice cooling, 60% sodium hydride (75 g) was suspended

in toluene (1400 ml) and heated to a reaction temperature of 110°C. Then a portion (30 ml) of a solution of bis-(methylpropionyl)-4-fluorophenethylamine (263.52 g) in toluene (100 ml) was added dropwise thereinto. Subsequently, methanol (3.2 ml) was added dropwise into the resultant mixture to cause a little evolution of gas and then the mixture was stirred at room temperature until the evolution was ceased. The reaction solution was heated again and a portion (5 ml) of the above solution of bis(methylpropionyl)-4-fluorophenethyl-amine (263.52 g) in toluene (100 ml) was added dropwised thereinto. After the completion of the addition, the resultant mixture was stirred for 30 min and then ice cooled. After adding water (800 ml), the precipitate was collected by filtration, washed with water (700 ml), toluene (500 ml) and hexane (500 ml) and dried to give the title compound (255.0 g) as pale yellow crystals (yield: quantitative).

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.96(2H, t, J=6.0Hz), 2.51(2H, m), 2.72(2H, t, J=7.6Hz), 3.15(2H, s), 3.39(3H, s), 7.08(2H, t, J=8.8Hz), 7.26(2H, dd, J=6.0, 8.8Hz).

(40-3) 1-Fluorophenethyl-4-piperidone

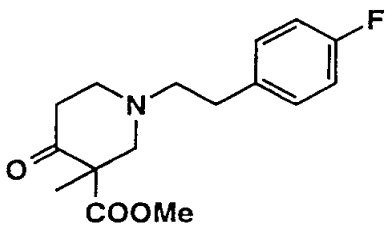


Hydrochloric acid (500 ml) and toluene (500 ml) were added to 1-fluorophenethyl-3-methoxycarbonyl-4-piperidone (sodium salt) and the resultant mixture was heated under reflux at 130°C for 15.5 hr. Then the reaction solution was ice cooled and basified by adding sodium hydroxide. Next, it was extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and filtered through silica gel. After concentrating the filtrate under reduced pressure, the residue was diluted with hexane (500 ml) and isopropyl ether (500 ml) and stirred under ice cooling for 1 hr. The resulting crystalline precipitates were collected by filtration, washed with cold hexane and then dried to give the title compound (133.67 g) as pale yellow crystals (yield: 71.4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.48(4H, t, J=6.2Hz), 2.70(2H, m), 2.80(2H, m), 2.82(4H, t, J=6.2Hz), 6.98(2H, t, J=8.8Hz), 7.17(2H, dd, J=5.2, 8.8Hz).

(40-4) Methyl 1-[2-(4-fluorophenyl)ethyl]-3-methyl-4-oxo-3-piperidinecarboxylate



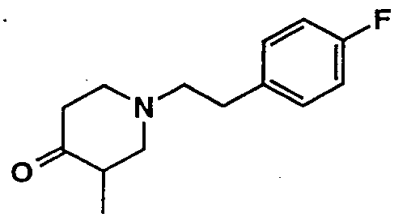
Sodium salt (15.1 g) of methyl 1-[2-(4-fluorophenyl)-

ethyl]-4-oxo-3-piperidinecarboxylate was dissolved in dimethylformamide (150 ml). Under ice cooling, methyl iodide (3.1 ml) was added thereto and the resultant mixture was stirred at room temperature overnight. Then ice water (500 ml) was added and the resultant mixture was extracted with ether (200 ml) twice. The organic layer was washed with water (100 ml) and brine (100 ml), dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (Fuji Silysia NH-DM2035, hexane/ethyl acetate system) to give the title compound (3.4 g) as a pale yellow liquid (yield: 23%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.26(3H, s), 2.16(1H, d, J=11.5Hz), 2.45(2H, m), 2.66(2H, m), 2.78(2H, m), 2.87(1H, m), 3.09(1H, m), 3.57(1H, dd, J=3.0Hz, 11.5Hz), 3.70(3H, s), 6.97(2H, br-t), 7.17(2H, br-d).

(40-5) 1-[2-(4-Fluorophenyl)ethyl]-3-methyl-4-piperidone



Conc. hydrochloric acid (12 ml) was added to a solution (12 ml) of methyl 1-[2-(4-fluorophenyl)ethyl]-3-methyl-4-oxo-3-piperidinecarboxylate (3.4 g) in toluene followed by

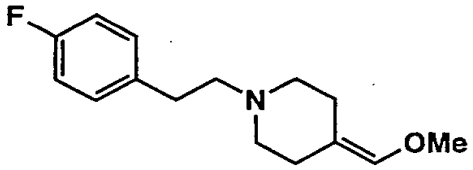
heating under reflux for 2.5 hr. The reaction mixture was cooled and added under ice cooling to a 1.5 N aqueous solution (100 ml) of sodium hydroxide. Further, the pH value of the mixture was regulated to 9 with a 5 N aqueous solution of sodium hydroxide. After extracting with ethyl acetate (100 ml) twice, the organic layer was washed with water (100 ml) and brine (100 ml), dried and concentrated under reduced pressure to give the title compound (2.87 g) as a pale yellow liquid (yield: 100%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.02(3H, d, J=7Hz), 2.16(1H, t, J=10Hz), 2.37(2H, m), 2.45(1H, m), 2.58(1H, m), 2.65(2H, m), 2.81(2H, t, J=7Hz), 3.17(2H, m), 6.97(2H, br-t), 7.16(2H, br-d).

Production Example 41 Synthesis of 1-fluorophenethyl-4-formylpiperidine

(41-1) 1-Fluorophenethyl-4-methoxylidenepiperidine



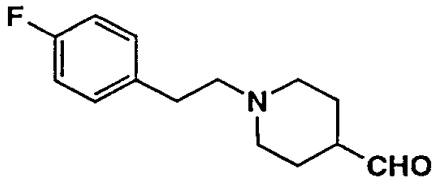
Methoxymethyltriphenylphosphonium chloride (36.3 g) was suspended in tetrahydrofuran (105 ml) and ice cooled. To the resultant suspension were successively added potassium t-butoxide (11.9 g) and 1-fluorophenethyl-4-piperidone (7.8 g) dissolved in tetrahydrofuran (105 ml) and the resultant mixture was stirred at room temperature. After adding water and ethyl

acetate to the reaction solution, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (7.41 g) as a yellow oil (yield: 84.2%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.12(2H, t, J=5.6Hz), 2.36(2H, t, J=5.6Hz), 2.49(4H, m), 2.57(4H, m), 2.79(4H, m), 3.55(3H, m), 5.81(1H, d, J=1.2Hz), 6.96(2H, t, J=8.8Hz), 7.15(2H, dd, J=5.6, 8.8Hz).

(41-2) 1-Fluorophenethyl-4-formylpiperidine



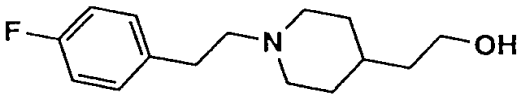
1-Fluorophenethyl-4-methylidenepiperidine (1.0 g) was dissolved in 1 N hydrochloric acid followed by stirring at 70°C for 4 hr. After allowing to cool, the solution was neutralized with a 5 N aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (0.240 g) as a pale yellow oil (yield: 25.4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 0.72-1.82(2H, m), 1.95-2.01(2H, m), 2.23-2.34(3H,

m), 2.59-2.63(2H, m), 2.90-2.95(2H, m), 6.96(2H, t, J=8.4Hz), 7.15(2H, dd, J=5.6 ,8.4Hz).

Production Example 42 Synthesis of 1-(4-fluorophenethyl)-4-piperidineethanol

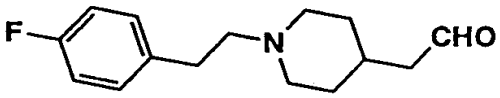


4-Piperidineethanol (3.2 g) and 4-fluorophenethyl bromide (5.0 g) were treated as in Example 2 to give the title compound (4.1 g) as a colorless oil (yield: 65%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.22-1.38(2H, m), 1.40-1.60(3H, m), 1.70-1.79(2H, m), 1.91-2.02(3H, m), 2.50-2.59(2H, m), 2.78-2.81(2H, m), 2.95-3.01(2H, m), 3.69-3.75(2H, m), 6.91-7.00(2H, m), 7.10-7.20(2H, m).

Production Example 43 Synthesis of 1-(4-fluorophenethyl)-4-piperidinacetaldehyde



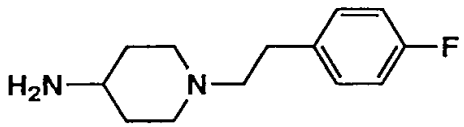
A suspension of 1-(4-fluorophenethyl)-4-piperidine-ethanol (1.0 g), pyridinium chlorochromate (2.6 g) and molecular sieve (2.0 g) in methylene chloride (60 ml) was stirred at room temperature for 1 hr. Then the reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel

column chromatography (methanol/ethyl acetate system) to give the title compound (360 mg) (yield: 36%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.29-1.43(2H, m), 1.69-1.80(2H, m), 1.81-2.10(3H, m), 2.33-2.42(2H, m), 2.50-2.60(2H, m), 2.72-2.80(2H, m), 2.93-3.00(2H, m), 6.93-7.00(2H, m), 7.10-7.20(2H, m), 9.78-9.80(1H, m).

Production Example 44 Synthesis of 1-(4-fluorophenethyl)-4-aminopiperidine



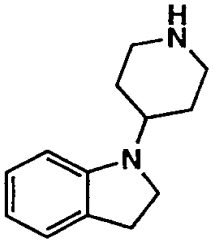
A suspension of 1-(4-fluorophenethyl)-4-piperidone (5.0 g), hydroxylammonium chloride (1.9 g) and anhydrous sodium acetate (4.4 g) in ethanol (50 ml) was heated under reflux for 30 min. The reaction solution was then concentrated under reduced pressure, diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the residue was diluted with tetrahydrofuran (50 ml) and lithium aluminum hydride (1.7 g) was added thereto in portions under ice cooling and stirring followed by heating under reflux for 4 hr. Under cooling with ice water, water (1.7 ml), a 5 N aqueous

solution of sodium hydroxide (5.1 ml) and further water (1.7 ml) were carefully added to the reaction solution in this order and the resultant mixture was stirred vigorously. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure and purified by NH-silica gel column chromatography (methylene chloride/methanol system) to give the title compound (4.0 g) as a pale yellow oil (yield: 80%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.31-1.60(4H, m), 1.80-1.89(2H, m), 2.01-2.11(2H, m), 2.50-2.58(2H, m), 2.63-2.81(3H, m), 2.91-3.00(2H, m), 6.94-7.03(2H, m), 7.14-7.25(2H, m).

Production Example 45 Synthesis of 1-(piperidin-4-yl)-indoline



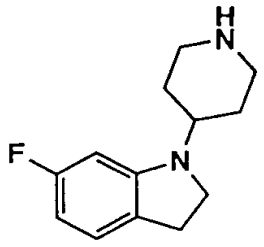
A mixture of indoline (25 g), 1-acetyl-4-piperidone (25 g), platinum oxide (0.5 g), acetic acid (20 ml) and ethanol (200 ml) was catalytically reduced at ordinary temperature under atmospheric pressure overnight. After filtering off the catalyst, the filtrate was concentrated under reduced pressure and diluted with a 2 N aqueous solution of sodium hydroxide and

ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and purified by silica gel column chromatography (methylene chloride/ethanol system). To the obtained residue was added 5 N hydrochloric acid (300 ml) followed by heating the mixture under reflux for 2 hr. Then the reaction solution was basified with a conc. aqueous solution of sodium hydroxide, diluted with ethyl acetate and the layers were separated. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (26 g) as brown crystals (yield: 61%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.51-1.69(3H, m), 1.80-1.85(2H, m), 2.66-2.72(2H, m), 2.91(2H, t, J=8Hz), 3.11-3.22(2H, m), 3.39(2H, t, J=8Hz), 3.40-3.52(1H, m), 6.41(1H, d, J=8Hz), 6.60(1H, d, J=8Hz), 7.01-7.10(2H, m).

Production Example 46 Synthesis of 1-(piperidin-4-yl)-6-fluoroindoline



1-Chloroethyl chloroformate (2.8 g) was added dropwise into a solution of 1-(1-benzylpiperidin-4-yl)-6-

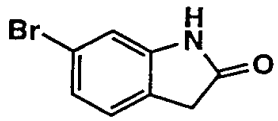
fluoroindoline (2.0 g) in toluene (50 ml) followed by heating the mixture under reflux for 2 hr. Then the reaction solution was concentrated under reduced pressure and methanol was added thereto followed by heating under reflux again for 2 hr. After concentrating under reduced pressure, a 5 N aqueous solution of sodium hydroxide and chloroform were added thereto, the layers were separated. The organic layer was then washed with brine and dried over anhydrous magnesium sulfate to give the title compound (1.0 g) as a brown oil (yield: 70%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.59-1.71(2H, m), 1.80-1.87(2H, m), 2.06(1H, br-s), 2.68-2.75(2H, m), 2.91(2H, t, J=8Hz), 3.20-3.29(2H, m), 3.34-3.48(1H, m), 3.45(2H, t, J=8Hz), 6.08(1H, d, J=8Hz), 6.23(1H, t, J=8Hz), 6.91(1H, t, J=8Hz).

Production Example 47 Synthesis of 6-bromoindoline

(47-1) 6-Bromo-2-oxyindole



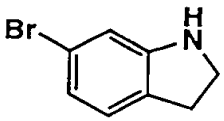
Under ice cooling, diethyl malonate (500 g) was added dropwise into a suspension of sodium hydride (125 g) in dimethyl sulfoxide (800 ml). After the solution became homogeneous, the resultant mixture was heated to 100°C and a solution of 2,5-dibromonitrobenzene (500 g) in dimethyl sulfoxide (400 ml) was added dropwise thereinto followed by stirring the resultant

mixture at 100°C for 5 hr. Then the reaction solution was diluted with ice water (2 l), mixed with ethyl acetate (8 l), and the layers were separated. The organic layer was washed successively with water (2 l) four times and brine and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the residue was diluted with ethanol (2.5 l) followed by the addition of tin (380 g). Under ice cooling, conc. hydrochloric acid (1.5 l) was added dropwise into the reaction mixture. After the completion of the addition, the resultant mixture was heated under reflux for 3 hr and diluted with ice water (8 l). The resulting crystalline precipitates were collected by filtration, washed with water and hexane, and air dried at 50°C for 24 hr to give the title compound (321 g) (yield: 84%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.51(2H, s), 7.06(1H, s), 7.10(1H, d, J=8Hz), 7.17(1H, d, J=8Hz), 8.27(1H, br-s).

(47-2) 6-Bromoindoline



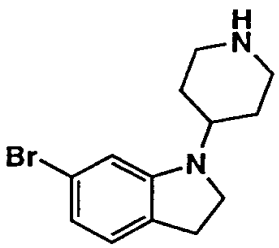
Under ice cooling, a borane/methyl sulfide complex (300 ml) was added dropwise into a suspension of 6-bromo-2-oxyindole (311 g) in toluene (1 l). Then the resultant mixture was slowly heated under reflux. After 2 hr, it was ice cooled followed

by the addition thereto of a 5 N aqueous solution of sodium hydroxide (500 ml), an 8 N aqueous solution of sodium hydroxide (500 ml) and ethyl acetate (400 ml). After vigorously stirring for 1 hr, it was diluted with ethyl acetate (1.6 l) and water (1 l) and the layers were separated. The organic layer was washed successively with water (1 l) twice and brine (0.5 l) and dried over anhydrous magnesium sulfate. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (169 g) (yield: 58%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.96(2H, t, J=8Hz), 3.58(2H, t, J=8Hz), 6.76(1H, s), 6.80(1H, d, J=8Hz), 6.95(1H, d, J=8Hz).

Production Example 48 Synthesis of 1-(piperidin-4-yl)-6-bromoindoline



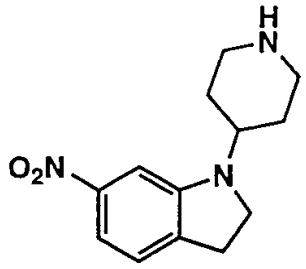
1-Chloroethyl chloroformate (13.7 g) was added dropwise into a solution of 1-(1-benzylpiperidin-4-yl)-bromoindoline (14.3 g) in toluene (250 ml) and the resultant mixture was heated under reflux for 2 hr. Then it was concentrated under reduced pressure and methanol was added thereto followed by heating under reflux for 2 hr. After concentrating under reduced

pressure, a 5 N aqueous solution of sodium hydroxide and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate to give the title compound (8.4 g) as a brown oil (yield: 78%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.51-1.69(2H, m), 1.78-1.83(2H, m), 2.06(1H, br-s), 2.67-2.73(2H, m), 2.90(2H, t, J=8Hz), 3.19-3.23(2H, m), 3.31-3.43(1H, m), 3.41(2H, t, J=8Hz), 6.49(1H, s), 6.68(1H, t, J=8Hz), 6.85(1H, t, J=8Hz).

Production Example 49 Synthesis of 1-(piperidin-4-yl)-6-nitroindoline



70% nitric acid (2.6 ml) was added dropwise at -15°C into a solution of 1-(piperidin-4-yl)indoline (6.9 g) in conc. sulfuric acid (50 ml). After 20 min, the reaction mixture was diluted with ice water and basified with a conc. aqueous solution of sodium hydroxide, the reaction solution was mixed with ethyl acetate, and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the

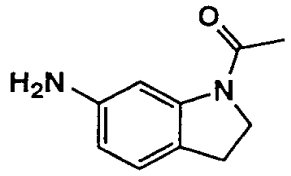
title compound (7 g) as a brown oil (yield: 83%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.53-1.69(3H, m), 1.75-1.83(2H, m), 2.69-2.78(2H, m), 3.03(2H, t, J=8Hz), 3.16-3.23(2H, m), 3.44-3.51(1H, m), 3.52(2H, t, J=8Hz), 7.08(1H, d, J=8Hz), 7.10(1H, s), 7.48(1H, d, J=8Hz).

Production Example 50 Synthesis of 6-dimethylaminoindoline

(50-1) 1-Acetyl-6-aminoindoline



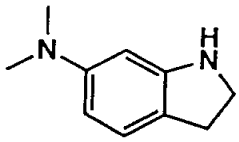
Fuming nitric acid (11 ml) was added dropwise at -15°C into a solution of indoline (26.5 g) in conc. sulfuric acid (250 ml). After 20 min, the resultant mixture was diluted with ice water and washed with ethyl acetate. The aqueous phase was basified with a conc. aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. To the residue were added acetic anhydride (100 ml) and pyridine (100 ml) and the reaction mixture was stirred at room temperature for 4 hr. After adding ice water to the reaction solution, the resulting crystalline precipitates were collected by filtration and mixed with an iron powder (40 g), ammonium chloride (60 g), water (70 ml) and ethanol (300 ml).

The resultant mixture was stirred at 60°C overnight followed by filtration and concentration under reduced pressure. After adding water, the resultant mixture was stirred vigorously. The resulting crystalline precipitates were collected by filtration and air dried at 70°C overnight to give the title compound (19 g) as a brown powder (yield: 57%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.20(3H, s), 3.08(2H, t, J=8Hz), 3.63(2H, br-s), 4.01(2H, t, J=8Hz), 6.33(1H, d, J=8Hz), 6.91(1H, d, J=8Hz), 7.67(1H, s).

(50-2) 6-Dimethylaminoindoline



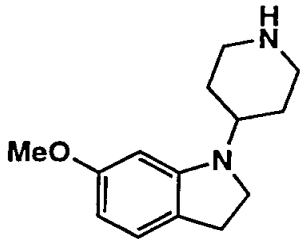
A mixture of 1-acetyl-6-aminoindoline (1.0 g), 37% formaldehyde (5.2 g), acetic acid (1.0 ml), platinum oxide (0.1 g) and methanol (20 ml) was catalytically reduced at ordinary temperature under atmospheric pressure. After a day, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography

(methylene chloride/ethanol system). To the obtained residue was added 5 N hydrochloric acid (30 ml) followed by heating the resultant mixture under reflux for 1 hr. Then the reaction solution was basified with a conc. aqueous solution of sodium hydroxide and extracted with chloroform. After purifying by silica gel column chromatography (hexane/ethyl acetate system), the title compound (0.6 g) was obtained as a brown powder (yield: 65%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.89(6H, s), 2.91(2H, t, J=8Hz), 3.52(2H, t, J=8Hz), 3.70(1H, br-s), 6.11(1H, d, J=8Hz), 6.12(1H, s), 6.95(1H, d, J=8Hz).

Production Example 51 Synthesis of 1-(piperidin-4-yl)-6-methoxyindoline



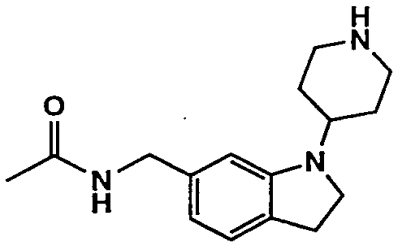
1-Chloroethyl chloroformate (10.5 g) was added dropwise into a solution of 1-(1-benzylpiperidin-4-yl)-6-methoxyindoline (7.9 g) in toluene (200 ml) and the resultant mixture was heated under reflux for 3 hr. Then it was concentrated under reduced pressure and methanol was added thereto followed by heating the resultant mixture under reflux

for 2 hr. After concentrating under reduced pressure, a 5 N aqueous solution of sodium hydroxide and chloroform were added thereto, and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate to give the title compound (4.1 g) as a brown oil (yield: 72%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.51-1.62(2H, m), 1.78-1.85(2H, m), 1.92(1H, br-s), 2.62-2.74(2H, m), 2.89(2H, t, J=8Hz), 3.13-3.22(2H, m), 3.34-3.46(1H, m), 3.40(2H, t, J=8Hz), 3.76(3H, s), 6.00(1H, s), 6.11(1H, d, J=8Hz), 6.93(1H, d, J=8Hz).

Production Example 52 Synthesis of 1-(piperidin-4-yl)-6-acetamidomethylindoline



Under ice cooling, acetyl chloride (1.7 ml) was added dropwise into a solution of 1-[1-(4-t-butoxycarbonyl)piperidin-4-yl]-6-aminomethylindoline (8.3 g) and triethylamine (2.4 g) in acetonitrile (150 ml) followed by stirring the resultant mixture at room temperature for 1 hr. To the liquid reaction mixture were added a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was then washed with brine,

dried over anhydrous magnesium sulfate and concentrated under reduced pressure. After adding chloroform (100 ml) and trifluoroacetic acid (50 ml), the resultant mixture was stirred at room temperature for 2 hr. After concentrating under reduced pressure, a 2 N aqueous solution of sodium hydroxide (100 ml) and toluene (50 ml) were added thereto followed by vigorous stirring. Then the resultant mixture was purified by NH-silica gel column chromatography (methanol/ethyl acetate system) to give the title compound (3.78 g) as white needles (yield: 58%).

m.p.: 165-167°C

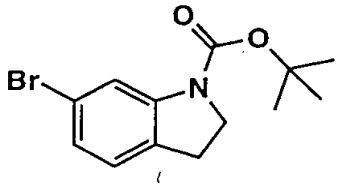
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.64-1.86(4H, m), 2.52-2.82(2H, m), 2.93(2H, t, J=8Hz), 3.24-3.32(2H, m), 3.42(2H, t, J=8Hz), 3.44-3.52(1H, m), 4.33(2H, d, J=5Hz), 5.67(1H, br-s), 6.34(1H, s), 6.51(1H, d, J=8Hz), 7.00(1H, d, J=8Hz).

FAB-Mass: 274(MH^+)

<u>Production Example 53 Synthesis of 6-(N-methylsulfamoyl-methyl)indoline</u>

<u>(53-1) 1-t-butoxycarbonyl-6-bromoindoline</u>



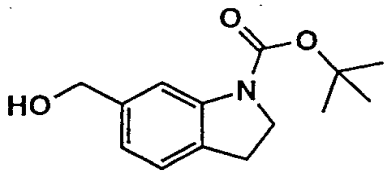
Di-t-butyl carbonate (6.7 g) was added to a solution of 6-bromoindoline (5.1 g) and triethylamine (3.1 g) in

tetrahydrofuran (50 ml) followed by stirring the resultant mixture at room temperature overnight. After adding water and ethyl acetate thereto, the layers were separated and the organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was then purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (5.5 g) as a colorless oil (yield: 71%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.56(9H, s), 3.04(2H, t, J=8Hz), 3.99(2H, t, J=8Hz), 6.98(1H, d, J=8Hz), 7.03(1H, d, J=8Hz), 8.04(1H, s).

(53-2) 1-t-Butoxycarbonyl-6-hydroxymethylindoline



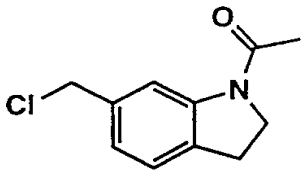
A 2.5 M solution (7 ml) of n-butyllithium in hexane was added dropwise at -78°C into a solution of 1-t-butoxycarbonyl-6-bromoindoline (3.5 g) in tetrahydrofuran (100 ml) over 5 min. After 10 min, dimethylformamide (1.4 ml) was added thereto and the resultant mixture was heated to room temperature. After adding a saturated aqueous solution of ammonium chloride and ethyl acetate thereto, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. Then ethanol (20 ml) and sodium borohydride (0.4 g)

were added to the residue followed by stirring the resultant mixture at room temperature for 1 hr. After adding ice water and ethyl acetate to the reaction solution, the organic layer was separated, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.9 g) as a colorless oil (yield: 66%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.60(9H, s), 3.08(2H, t, J=8Hz), 3.99(2H, t, J=8Hz), 4.68(2H, s), 6.95(1H, d, J=8Hz), 7.12(1H, d, J=8Hz), 7.87(1H, s).

(53-3) 1-Acetyl-6-chloromethylindoline



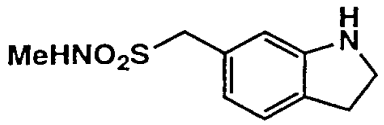
A solution of 1-t-butoxycarbonyl-6-hydroxymethyl-indoline (1.9 g) in conc. hydrochloric acid (20 ml) was stirred at 50°C overnight. Then it was basified by adding a conc. aqueous solution of sodium hydroxide. After adding ethyl acetate (40 ml) and acetyl chloride (0.5 ml), the resultant mixture was stirred at room temperature for 1 hr. The organic layer was separated, washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by silica gel

column chromatography (hexane/ethyl acetate system) to give the title compound (0.87 g) as a colorless oil (yield: 54%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.23(3H, s), 3.20(2H, t, J=8Hz), 4.09(2H, t, J=8Hz), 4.59(2H, s), 7.06(1H, d, J=8Hz), 7.16(1H, d, J=8Hz), 8.25(1H, s).

(53-4) 6-(N-Methylsulfamoylmethyl)indoline



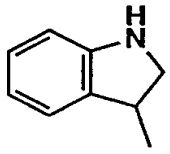
A solution of 1-acetyl-6-chloromethylindoline (470 mg), sodium sulfite (330 mg) and tricaprylylmethylammonium chloride (50 mg) in water (30 ml) was heated under reflux for 1 hr and then concentrated under reduced pressure. To the residue were added phosphorus pentaoxide (500 mg) and phosphorus oxychloride (5 ml) followed by stirring the resultant mixture at room temperature for 3 hr. Next, ice water and ethyl acetate were added to the reaction solution, the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. After concentrating under reduced pressure, a 2 M solution of methylamine in tetrahydrofuran (20 ml) was added to the residue followed by stirring the mixture at room temperature overnight. After adding a saturated aqueous solution of sodium bicarbonate and ethyl acetate to the reaction solution, the layers were separated and the organic layer was

washed with brine and dried over anhydrous magnesium sulfate. After concentrating under reduced pressure, the crystalline precipitates were collected, washed with ethanol and dissolved in 5 N hydrochloric acid (5 ml) followed by heating under reflux for 1 hr. Under ice cooling, the pH value of the reaction solution was adjusted to pH 8 with a conc. aqueous solution of sodium hydroxide, chloroform was added and the layers were separated. Then the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure to give the title compound (100 mg) as white crystals (yield: 20%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.71(3H, s), 3.01(2H, t, J=8Hz), 3.20(1H, br-s), 3.58(2H, t, J=8Hz), 4.15(2H, s), 4.25(1H, br-s), 6.65-6.69(2H, m), 7.08(1H, d, J=8Hz).

Production Example 54 Synthesis of 3-methylindoline



3-Methylindole (1.0 g) was dissolved in trifluoroacetic acid (30 ml). Under ice cooling, triethylsilane (2.4 ml) was added dropwise thereinto followed by stirring for 1 hr. After concentrating under reduced pressure, a saturated aqueous solution of sodium bicarbonate and ethyl acetate were added

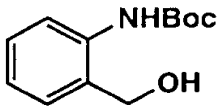
thereto, the layers were separated. Next, the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.673 g) as a pale yellow oil (yield: 66.3%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.32(3H, d, J=6.8Hz), 3.11(1H, t, J=8.6Hz), 3.36(1H, m), 3.70(1H, t, J=8.6Hz), 6.65(1H, d, J=8.0Hz), 6.73(1H, t, J=8.0Hz), 7.03(1H, t, J=8.0Hz), 7.09(1H, d, J=8.0Hz).

Production Example 55 Synthesis of 3-(4-fluorophenyl)-indoline

(55-1) 2-(t-Butoxy)carbonylaminobenzyl alcohol

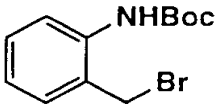


2-Aminobenzyl alcohol (5 g) was treated as reported in Synthesis, 871 (1991). to give the title compound (5.776 g) as a pale yellow oil (yield: 60.4%).

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.52(9H, s), 4.69(2H, s), 7.02(1H, t, J=8.0Hz), 7.17(1H, d, J=8.0Hz), 7.31(1H, t, J=8.0Hz), 7.63(1H, m), 7.91(1H, d, J=8.0Hz).

(55-2) 2-(t-Butoxy)carbonylaminobenzyl bromide

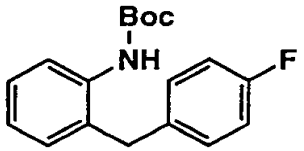


To 2-(t-butoxy)carbonylaminobenzyl alcohol (4.93 g) was added triethylamine (0.58 ml) followed by the same reaction as the one described in the above Production Example 1. Then the reaction solution was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (5.380 g) as pale yellow crystals (yield: 86.1%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.58(9H, s), 4.51(2H, s), 6.68(1H, m), 7.06(1H, t, J=8.0Hz), 7.28(1H, d, J=8.0Hz), 7.34(1H, t, J=8.0Hz), 7.84(1H, d, J=8.0Hz).

(55-3) 2-(4-Fluorobenzyl)-N-(t-butoxy)carbonylaniline

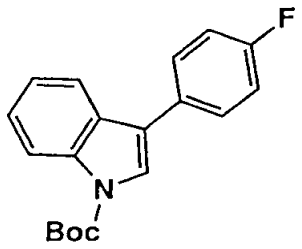


2-(t-Butoxy)carbonylaminobenzyl bromide (2.98 g) and 4-phenylmagnesium bromide were treated as reported in J. Organomet. C. 329, 133 - 138 (1987). to give the title compound (1.187 g) as pale yellow crystals (yield: 39.4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.46(9H, s), 3.93(2H, s), 6.12(1H, m), 6.91-7.12(7H, m), 7.82(1H, br-d).

(55-4) 1-(t-Butoxy)carbonyl-3-(4-fluorophenyl)indole

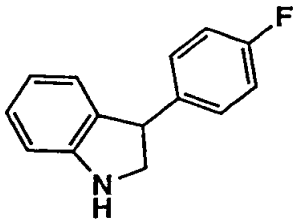


2-(4-Fluorobenzyl)-N-(t-butoxy)carbonylaniline (0.5 g) was treated as reported in Synthesis, 871 (1991). to give the title compound (0.340 g) as a pale yellow oil (yield: 68.2%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.69(9H, s), 7.15(2H, t, J=8.8Hz), 7.29(1H, t, J=8.0Hz), 7.37(1H, t, J=8.0Hz), 7.59(2H, dd, J=6.0, 8.8Hz), 7.67(1H, s), 7.75(1H, d, J=8.0Hz), 8.22(1H, d, J=8.0Hz).

(55-5) 3-(4-Fluorophenyl)indoline



1-(t-Butoxy)carbonyl-3-(4-fluorophenyl)indole (0.340 g) was freed from the protecting group with the use of trifluoroacetic acid and then treated as in the above Production Example 54 to give the title compound (0.184 g) as a pale yellow oil (yield: 79.0%).

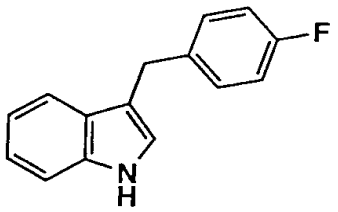
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.45(1H, t, J=8.8Hz), 3.92(1H, t, J=8.8Hz), 4.48(1H,

t, J=8.8Hz), 6.72(2H, m), 6.89(1H, d, J=8.4Hz), 6.99(2H, t, J=8.4Hz), 7.08(1H, t, J=8.4Hz), 7.23(2H, m).

Production Example 56 Synthesis of 3-(4-fluorobenzyl)-indoline

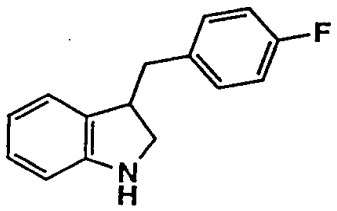
(56-1) 3-(4-Fluorobenzyl)indole



3-Formylindole was treated as reported in Tetrahedron Lett., 1869 (1986). to give the title compound as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 4.05(2H, s), 6.84(1H, s), 6.93(2H, t, J=8.4Hz), 7.06(1H, t, J=8.0Hz), 7.15-7.19(3H, m), 7.46(1H, d, J=8.0Hz), 7.97(1H, m).

(56-2) 3-(4-Fluorobenzyl)indoline



3-(4-Fluorobenzyl)indole (2.119 g) was dissolved in trifluoroacetic acid (3.9 ml). Under ice cooling, a 1.0 M solution (18.7 ml) of a borane/tetrahydrofuran complex in tetrahydrofuran was dropped into the above solution followed

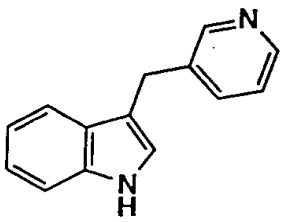
by stirring the resultant mixture at room temperature for 1 hr. After adding water, the reaction solution was concentrated under reduced pressure. Then ethanol (20 ml) and a 5 N aqueous solution (46 ml) of sodium hydroxide were added and the resultant mixture was stirred at room temperature for 1 hr. After adding ethyl acetate (200 ml) thereto, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.163 g) as a yellow oil (yield: 54.4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.80(1H, dd, J=8.0, 13.6Hz), 3.06(1H, dd, J=4.6, 13.6Hz), 3.26(1H, m), 3.55(2H, m), 6.48-6.71(2H, m), 6.92(1H, t, J=7.6Hz), 6.99(2H, t, J=8.8Hz), 7.05(1H, t, J=7.6Hz), 7.15(1H, dd, J=5.6, 8.8Hz).

Production Example 57 Synthesis of 3-(3-pyridylmethyl)-indoline

(57-1) 3-(3-Pyridylmethyl)indole



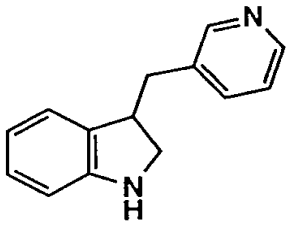
3-Bromopyridine was treated as reported in Tetrahedron

Lett., 1869 (1986). to give the title compound as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 4.11(2H, s), 6.92(1H, s), 7.09(1H, t, J=8.0Hz), 7.18(2H, m), 7.46(1H, d, J=8.0Hz), 7.48(1H, d, J=8.0Hz), 7.54(1H, d, J=8.0Hz), 8.33(1H, m), 8.45(1H, m), 8.60(H, m).

(57-2) 3-(3-Pyridylmethyl)indoline



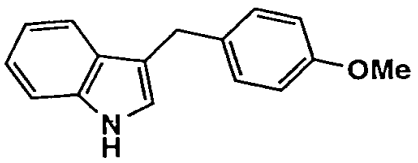
3-(3-Pyridylmethyl)indole (0.212 g) was treated as in the above Production Example 56-2 to give the title compound (0.253 g) as a yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.83(1H, m), 3.06(1H, m), 3.27(1H, d, J=3.2Hz), 3.56(2H, m), 6.50(1H, d, J=8.0Hz), 6.69(1H, t, J=8.0Hz), 6.92(1H, d, J=8.0Hz), 7.23(1H, m), 7.49(1H, d, J=8.0Hz), 8.48(1H, m).

Production Example 58 Synthesis of 3-(4-methoxybenzyl)-indoline

(58-1) 3-(4-Methoxybenzyl)indole

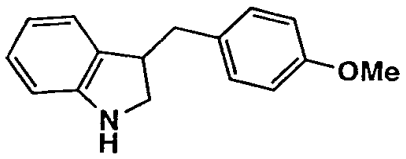


1-Diethylcarbamoyl-3-formylindole (7.33 g), which had been obtained according to the method of Tetrahedron Lett., 1869 (1986)., and 4-methoxyphenylmagnesium bromide were treated as reported in Tetrahedron Lett., 1869 (1986). to give the title compound (5.480 g) as a pale yellow oil (yield: 77.0%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.78(3H, s), 4.06(2H, s), 6.82(2H, d, J=6.8Hz), 6.90(1H, s), 7.07(1H, t, J=8.0Hz), 7.18(1H, t, J=8.0Hz), 7.20(2H, d, J=6.8Hz), 7.36(1H, d, J=8.0Hz), 7.51(1H, d, J=8.0Hz), 7.89(1H, m).

(58-2) 3-(4-Methoxybenzyl)indoline



3-(4-Methoxybenzyl)indole (0.5 g) was treated as in Production Example 54 to give the title compound (0.332 g) as a pale yellow oil (yield: 65.7%).

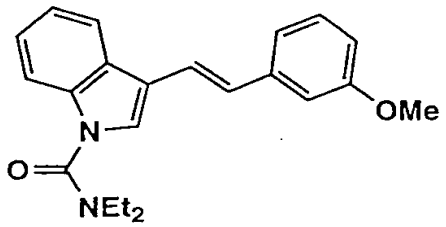
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.76(1H, dd, J=8.4, 14.0Hz), 3.04(1H, dd, J=5.2, 14.0Hz), 3.54(2H, m), 3.76(1H, d, J=5.2Hz), 3.81(3H, s), 6.65(1H, d, J=7.6Hz), 6.69(1H, t, J=7.6Hz), 6.85(2H, d, J=8.2Hz), 6.95(1H, d, J=7.6Hz), 7.04(1H, t, J=7.6Hz), 7.12(2H, d, J=8.2Hz).

Production Example 59 Synthesis of 3-(3-

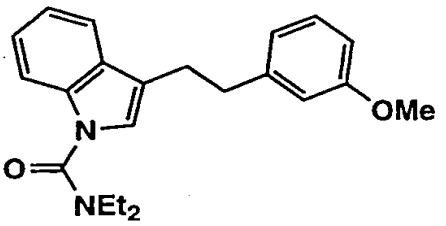
methoxyphenethyl)indoline

(59-1) 1-Diethylcarbamoyl-3-[2-(3-methoxyphenyl)vinyl]indole



3-Methoxybenzyltriphenylphosphonium chloride (1.71 g) and 1-diethylcarbamoyl-3-formylindole (1.71 g), which had been synthesized according to the method of Tetrahedron Lett., 1869 (1986)., were reacted in tetrahydrofuran (5 ml) as in the above Production Example 41-1 to give the title compound (0.842 g) as a brown oil (yield: 59.1%).

(59-2) 1-Diethylcarbamoyl-3-(3-methoxyphenethyl)indole



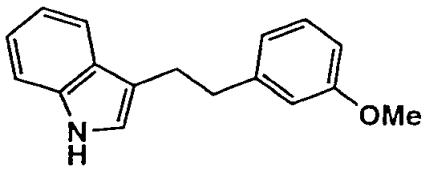
1-Diethylcarbamoyl-3-[2-(3-methoxyphenyl)vinyl]indole (0.842 g) was dissolved in methanol (20 ml) and catalytically reduced with the use of palladium carbon at room temperature under atmospheric pressure for 1 hr. After filtering off the catalyst, the filtrate was concentrated under reduced pressure to give the title compound (0.864 g) as a brown oil (yield:

quantitative).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.19(6H, t, J=7.2Hz), 3.01(4H, m), 3.42(4H, q, J=7.2Hz), 3.78(3H, s), 6.72(2H, m), 6.79(1H, d, J=8.4Hz), 6.95(1H, s), 7.18(2H, t, J=8.4Hz), 7.27(1H, m), 7.57(1H, d, J=8.4Hz), 7.63(1H, d, J=8.4Hz).

(59-3) 3-(3-Methoxyphenethyl)indole

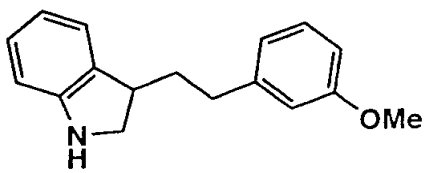


1-Diethylcarbamoyl-3-(3-methoxyphenethyl)indole (0.864 g) was deprotected as reported in Tetrahedron Lett., 7911 (1993). to give the title compound (0.554 g) as a brown oil (yield: 91.1%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.00(2H, m), 3.08(2H, m), 3.78(3H, s), 6.75(2H, m), 6.82(1H, d, J=8.0Hz), 6.93(1H, s), 7.12(1H, t, J=8.0Hz), 7.19(2H, q, J=8.0Hz), 7.36(1H, d, J=8.0Hz), 7.62(1H, d, J=8.0Hz), 7.93(1H, m).

(59-4) 3-(3-Methoxyphenethyl)indoline



3-(3-Methoxyphenethyl)indole (0.554 g) was treated as in

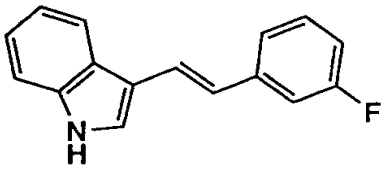
the above Production Example 56-2 to give the title compound (0.133 g) as a pale yellow oil (yield: 23.8%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.83(1H, m), 2.15(1H, m), 2.70(2H, t, J=8.0Hz), 3.34(1H, m), 3.71(2H, t, J=8.0Hz), 3.80(3H, s), 6.64(1H, d, J=8.0Hz), 6.75(3H, m), 6.80(1H, d, J=8.0Hz), 7.03(1H, t, J=8.0Hz), 7.10(1H, d, J=8.0Hz), 7.20(1H, t, J=8.0Hz).

Production Example 60 Synthesis of 3-(3-fluorophenethyl)-indoline

(60-1) 3-[2-(3-Fluorophenyl)vinyl]indole

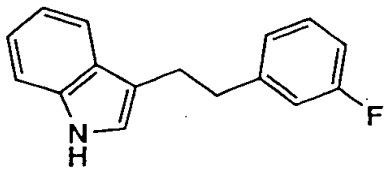


3-Formylindole (1.0 g) and 3-fluorobenzylphosphonium chloride (2.8 g) were treated as in the above Production Example 41-1 to give the title compound (0.598 g) as colorless crystals (yield: 73.1%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 6.51(1H, d, J=12.0Hz), 6.80(1H, d, J=12.0Hz), 6.89(1H, m), 7.06-7.37(7H, m), 7.47(1H, dd, J=0.4, 8.0Hz), 8.04(1H, m).

(60-2) 3-(3-Fluorophenethyl)indole

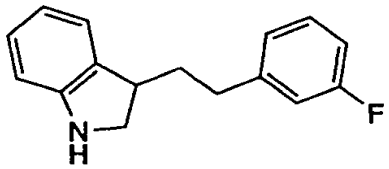


3-[2-(3-Fluorophenyl)vinyl]indole (0.598 g) was treated as in the above Production Example 59-2 to give the title compound (0.541 g) as a brown oil (yield: 89.7%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.04(4H, m), 6.90(2H, m), 6.98(1H, d, J=8.0Hz), 7.13(1H, dt, J=0.8, 8.0Hz), 7.23(2H, m), 7.36(1H, d, J=8.0Hz), 7.61(1H, dd, J=0.8, 8.0Hz), 7.89(1H, br-s).

(60-3) 3-(3-Fluorophenethyl)indoline

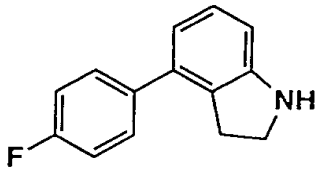


3-(3-Fluorophenethyl)indole (0.541 g) was treated as in the above Production Example 56-2 to give the title compound (0.582 g) as a brown oil (yield: quantitative).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.87(1H, m), 2.14(1H, m), 2.72(2H, t, J=8.0Hz), 3.26(2H, t, J=8.0Hz), 3.30(1H, m), 3.71(1H, t, J=8.0Hz), 6.65(1H, d, J=8.0Hz), 6.73(1H, t, J=8.0Hz), 6.88(2H, m), 7.03(1H, t, J=8.0Hz), 7.13(1H, d, J=8.0Hz), 7.23(1H, m).

Production Example 61 Synthesis of 4-(4-fluorophenyl)-indoline



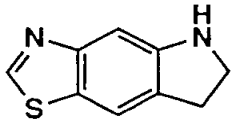
A mixture of 4-bromoindole (1.0 g), which had been synthesized according to the method of J. Org. Chem. (1986, Vol. 5, No. 26, p. 5106.), 4-fluorophenylboronic acid (1.1 g), tetrakis(triphenylphosphine)palladium (0.24 g), a 10% aqueous solution (10 ml) of sodium carbonate and toluene (20 ml) was heated under reflux for 4 hr. Then ethyl acetate was added to the reaction solution and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system). To the resulting residue was added trifluoroacetic acid (10 ml) and a 1 M solution (6.8 ml) of a borane/tetrahydrofuran complex in tetrahydrofuran followed by stirring the mixture at 0°C for 1 hr. After adding water, the resultant mixture was concentrated under reduced pressure. Then ethanol and an aqueous solution of sodium hydroxide were added thereto and the reaction mixture was stirred for 30 min. After adding ethyl acetate to the reaction solution, the layers were separated and the organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl

acetate system) to give the title compound (0.5 g) as a colorless oil (yield: 46%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.01(2H, t, J=8Hz), 3.50(2H, t, J=8Hz), 3.81(1H, br-s), 6.61(1H, d, J=8Hz), 6.72(1H, d, J=8Hz), 7.02-7.10(3H, m), 7.38-7.41(2H, m).

Production Example 62 Synthesis of thiazolo[5,4-f]indoline



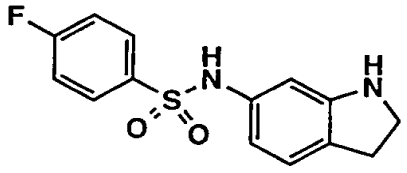
Bromine (2.5 ml) was added dropwise into a solution of 1-acetyl-6-aminoindoline (6.0 g) and potassium thiocyanate (9.3 g) in acetic acid (100 ml) followed by stirring the resultant mixture at room temperature for 5 hr. Under ice cooling, a 5 N aqueous solution of sodium hydroxide was added thereto and the crystalline precipitates were collected by filtration. Then these crystals were air dried at 60°C overnight and dissolved in dimethylformamide (90 ml). After adding isoamyl nitrite (18 ml) dropwise thereinto, the reaction mixture was stirred at 80°C for 1 hr followed by concentration under reduced pressure. Then a 5 N aqueous solution of sodium hydroxide and chloroform were added thereto and the layers were separated. The organic layer washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced

pressure. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system). After adding 5 N hydrochloric acid (150 ml), the mixture was heated under reflux for 30 min. Then a 5 N aqueous solution of sodium hydroxide and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine and dried over anhydrous magnesium sulfate. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.2 g) as brown powdery crystals (yield: 21%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 3.14(2H, t, J=8Hz), 3.65(2H, t, J=8Hz), 4.00(1H, br-s), 7.28(1H, s), 7.58(1H, s), 8.83(1H, s).

Production Example 63 Synthesis of 6-(4-fluorobenzene-sulfonylamino)indoline



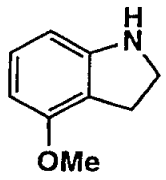
Under ice cooling, 4-fluorobenzenesulfonyl chloride (1.4 g) was added dropwise into a solution (10 ml) of 1-acetyl-6-aminoindoline (1.0 g) in pyridine followed by stirring the resultant mixture for 30 min. After concentrating it under reduced pressure, 5 N hydrochloric acid was added thereto and the resultant mixture was heated under reflux for 5 hr. Then

the reaction solution was basified with a conc. aqueous solution of sodium hydroxide and extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and purified by NH-silica gel column chromatography (methylene chloride/ethanol system) to give the title compound (1.36 g) as white powdery crystals (yield: 82%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.95(2H, t, J=8Hz), 3.64(2H, t, J=8Hz), 3.78(1H, br-s), 6.22(1H, d, J=8Hz), 6.33(1H, br-s), 6.48(1H, s), 6.90(1H, d, J=8Hz), 7.08-7.12(2H, m), 7.71-7.80(2H, m).

Production Example 64 Synthesis of 4-methoxyindoline



Under ice cooling, a 1 M solution (6.2 ml) of a borane/tetrahydrofuran complex in tetrahydrofuran was added dropwise into a solution of 4-methoxyindole (0.46 g) in trifluoroacetic acid (10 ml) followed by stirring the resultant mixture for 1 hr.

After adding water, the resultant mixture was concentrated under reduced pressure and ethanol and a 5 N aqueous solution of sodium hydroxide were added thereto followed by stirring the mixture overnight. After concentrating it under reduced pressure, the residue was extracted with ethyl acetate. The

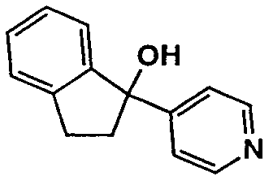
organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (130 mg) as a brown oil (yield: 28%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.95(2H, t, J=8Hz), 3.52(2H, t, J=8Hz), 3.80(1H, s), 6.28(1H, d, J=8Hz), 6.30(1H, d, J=8Hz), 6.99(1H, t, J=8Hz).

Production Example 65 Synthesis of 1-(piperidin-4-yl)indan

(65-1) 1-Hydroxy-1-(4-pyridyl)indan



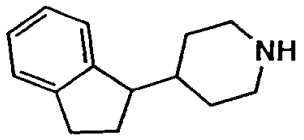
To 4-bromopyridine hydrochloride (19.4 g) were added a 2 N aqueous solution (120 ml) of sodium hydroxide and ether (300 ml) to extract 4-bromopyridine. Then the ether layer was dried over anhydrous potassium carbonate and cooled to -70°C. Into the resultant mixture was added dropwise 2.5 M n-butyllithium (40 ml) with stirring. After the completion of the addition, the reaction solution was stirred for 30 min and a solution (60 ml) of 1-indanone in ether was added thereto at -70°C. Then the reaction solution was allowed to warm to room temperature over 12 hr. Then it was pertitioned between ethyl acetate and a saturated aqueous solution of ammonium chloride. The ethyl

acetate layer was washed with water, dried and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (7.6 g) as a colorless oil (yield: 35.9%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 2.40-2.50(2H, m), 2.82(1H, br-s), 2.94-3.04(1H, m), 3.17-3.26(1H, m), 7.02(1H, d, J=8.4Hz), 7.22(1H, dt, J=8.4, 2.8Hz), 7.33(2H, d, J=8.0Hz), 7.30-7.37(2H, m), 8.47(2H, d, J=8.0Hz).

(65-2) 1-(Piperidin-4-yl)indan



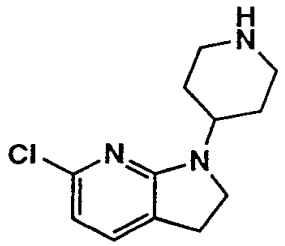
A mixture of 1-hydroxy-1-(4-pyridyl)indan (6.0 g), 6 N hydrochloric acid (20 ml) and ethanol (20 ml) was heated to 100°C for 30 min. Then the reaction solution was concentrated under reduced pressure and ethanol (200 ml) and platinum oxide (0.2 g) were added to the residue followed by hydrogenation under 3 kg/cm^2. After the completion of the reaction, the reaction solution was filtered through celite and extracted with ethanol. The filtrate was concentrated under reduced pressure and the residue was partitioned between ethyl acetate and a 2 N aqueous solution of sodium hydroxide. The ethyl acetate layer was washed with water, dried, concentrated under reduced pressure

and purified by NH-silica gel column chromatography (ethyl acetate) to give the title compound (4.2 g) as pale brown powdery crystals (yield: 73.4%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.13-1.49(3H, m), 1.51(1H, br-s), 1.62-1.70(1H, m), 1.72-1.82(1H, m), 1.90-2.00(1H, m), 2.02-2.18(1H, m), 2.50-2.64(2H, m), 2.75-2.92(2H, m), 3.01-3.13(3H, m), 7.09-7.21(4H, m).

Production Example 66 Synthesis of 1-(piperidin-4-yl)-6-chloro-7-azaindoline



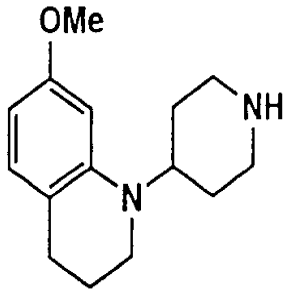
A mixture of 2,6-dichloro-3-formylmethylpyridine (5.6 g), ethyl 4-amino-1-piperidinecarboxylate (7.6 g), platinum oxide (140 mg), acetic acid (1.0 ml) and ethanol (100 ml) was catalytically reduced at ordinary temperature under atmospheric pressure in a stream of hydrogen. After 6 hr, the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was diluted with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate and then the

solvent was distilled off. The residue was purified by silica gel column chromatography (methylene chloride/ ethanol system). After adding triethylamine (1.5 g) and o-dichlorobenzene (100 ml), the resultant mixture was heated at 180°C for 2 hr. Then the reaction solution was concentrated under reduced pressure and diluted with a saturated aqueous solution of sodium hydrogencarbonate and ethyl acetate and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and purified by silica gel column chromatography (hexane/ethyl acetate system). After adding potassium hydroxide (10 g) and ethylene glycol (200 ml) to the residue, the resultant mixture was heated under reflux for 2 hr. Then the reaction solution was diluted with water and ethyl acetate and the layers were separated. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent the title compound (2.3 g) was obtained as a brown oil (yield: 33%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.71-1.89(4H, m), 2.80-2.91(2H, m), 2.94(2H, t, J=8Hz), 3.25-3.34(2H, m), 3.66(2H, t, J=8Hz), 4.11-4.23(1H, m), 6.38(1H, d, J=8Hz), 7.04(1H, d, J=8Hz).

Production Example 67 Synthesis of 1-(4-piperidinyl)-7-methoxy-1,2,3,4-tetrahydroquinoline

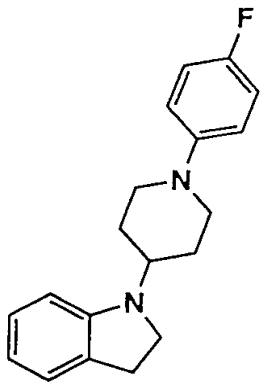


A solution of 1-(4-piperidinyl)-7-methoxy-3,4-dihydrocarbostyryl (1.50 g), which had been obtained by the method described in JP-A 3-173870, in THF (50 ml) was cooled to 0°C and lithium aluminum hydride (660 mg) was added thereto in five portions. The reaction mixture was stirred at 0°C for 10 min and then heated under reflux for 4 hr. After the completion of the reaction, the reaction mixture was cooled to 0°C and water (0.66 ml), a 5 N aqueous solution (0.66 ml) of sodium hydroxide and further water (2 ml) were successively added thereto. After further adding magnesium sulfate, the resultant mixture was stirred for 10 min. The resulting precipitate was filtered off through celite and the filtrate was concentrated to give the title compound (1.27 g) (yield: 89%).

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.62-1.91(6H, m), 2.02-2.12(1H, m), 2.64-2.75(3H

yl]indoline



Triacetoxylated sodium borohydride (760 mg) was added to a mixture of indoline (300 mg), 1-(4-fluorophenyl)-4-piperidone (580 mg), acetic acid (650 mg) and dichloroethane (30 ml), and the mixture was stirred for 2 hr. The obtained reaction solution was mixed with ethyl acetate and a saturated aqueous solution of sodium bicarbonate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (470 mg) as white prismatic crystals (yield: 63%).

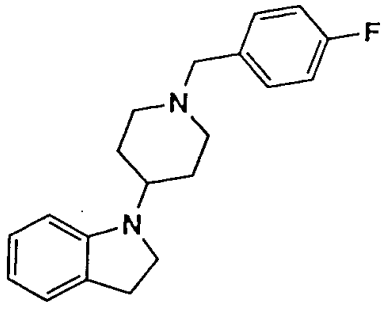
m.p.: 120 - 122°C.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.82-1.93(4H, m), 2.71-2.82(2H, m), 2.92-3.01(2H, m), 3.39-3.43(3H, m), 3.63-3.71(2H, m), 6.42-6.49(1H, m), 6.60-6.65(1H, m), 6.90-7.10(6H, m).

FAB-Mass: 297(MH+).

Example 2: Synthesis of 1-[1-(4-fluorobenzyl)piperidin-4-yl]indoline



4-Fluorobenzyl bromide (0.067 ml) was dissolved in N,N-dimethylformamide (2.5 ml). After adding 4-fluorobenzyl bromide (0.067 ml) and triethylamine (0.075 ml), the resulting mixture was stirred for 5 hr. Then water and ethyl acetate were added thereto and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.131 g) as colorless crystals (yield: 86.1%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride of the title compound was obtained as colorless crystals.

m.p. (hydrochloride): 223°C.

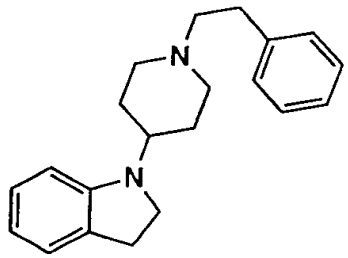
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.84(2H, br-d), 2.14(2H, m), 2.90(2H, t, J=8.4Hz), 3.01(2H, m), 3.33(2H, t, J=8.4Hz), 3.40(2H, br-d), 3.72(1H, m), 4.27(2H, d, J=4.8Hz), 6.62(1H, d, J=7.6Hz), 6.63(1H, t, J=7.6Hz), 7.02(1H, t, J=7.6Hz), 7.06(1H, d, J=7.6Hz), 7.31(2H, t, J=8.8Hz), 7.70(2H, dd, J=5.6, 8.8Hz).

ESI-Mass: 311.1(MH+).

Example 3: Synthesis of 1-(1-phenethylpiperidin-4-yl)indoline



(2-Bromoethyl)benzene (0.19 g) was treated as in Example 2 to give the title compound (0.126 g) as a colorless oil (yield: 77.3%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride of the title compound was obtained as colorless crystals.

m.p. (hydrochloride): 234°C.

Hydrochloride

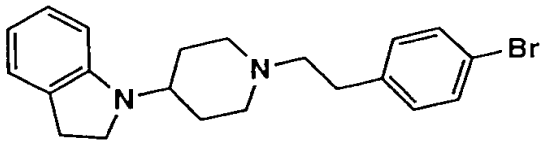
^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.89(2H, m), 2.10(2H, m), 2.91(2H, t, J=8.2Hz), 3.09(4H, m), 3.26(2H, m), 3.35(2H, t, J=8.2Hz), 3.65(2H, m),

3.76(1H, m), 6.60(1H, d, J=7.6Hz), 6.61(1H, t, J=7.6Hz), 7.02(1H, t, J=7.6Hz), 7.06(1H, d, J=7.6Hz), 7.28(3H, m), 7.35(2H, m).

FAB-Mass: 307(MH+).

Example 4: Synthesis of 1-[1-(4-bromophenethyl)piperidin-4-yl]indoline



4-Bromophenethyl bromide (0.1 g) was treated as in Example 2 to give the title compound (0.119 g) as a colorless oil (yield: 63.0%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride (0.110 g) of the title compound was obtained.

m.p. (hydrochloride): 230°C.

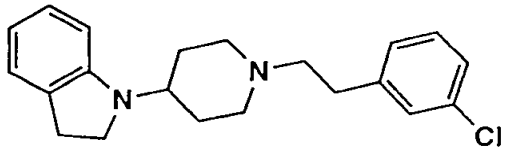
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.88(2H, br-d), 2.09(2H, m), 2.91(2H, t, J=8.2Hz), 3.09(4H, m), 3.25(2H, m), 3.36(2H, t, J=8.2Hz), 3.62(2H, br-d), 3.75(1H, m), 6.59(1H, d, J=8.0Hz), 6.60(1H, t, J=8.0Hz), 7.02(1H, t, J=8.0Hz), 7.05(1H, d, J=8.0Hz), 7.27(2H, d, J=8.4Hz), 7.55(2H, d, J=8.4Hz).

FAB-Mass: 385(MH+).

Example 5: Synthesis of 1-[1-(3-chlorophenethyl)piperidin-4-yl]indoline



3-Chlorophenethyl bromide (0.1 g) was treated as in Example 2 to give the title compound (0.119 g) as a colorless oil (yield: 63.0%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride (0.110 g) of the title compound was obtained. m.p. (hydrochloride): 219°C.

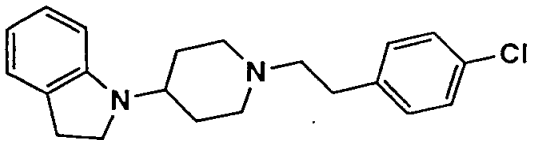
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.89(2H, br-d), 2.11(2H, m), 2.91(2H, t, J=8.4Hz), 3.09(4H, m), 3.27(2H, m), 3.35(2H, t, J=8.4Hz), 3.63(2H, br-d), 3.77(1H, br-t), 6.62(2H, m), 7.02(1H, t, J=8Hz), 7.06(1H, d, J=8Hz), 7.27(1H, d, J=7.2Hz), 7.32-7.41(3H, m).

FAB-Mass: 341(MH+).

Example 6 Synthesis of 1-[1-(4-chlorophenethyl)piperidin-4-yl]indoline



4-Chlorophenethyl bromide (0.1 g) was treated as in Example 2 to give the title compound (0.125 g) as a colorless oil (yield: 74.8%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride (0.120 g) of the title compound was obtained. m.p. (hydrochloride): 228°C.

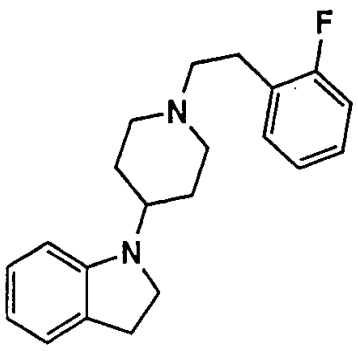
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.88(2H, br-d), 2.11(2H, m), 2.91(2H, t, J=8.4Hz), 3.09(4H, m), 3.25(2H, m), 3.35(2H, t, J=8.4Hz), 3.63(2H, br-d), 3.77(1H, br-t), 6.62(1H, d, J=8.0Hz), 6.63(1H, t, J=8.0Hz), 7.03(1H, t, J=8.0Hz), 7.06(1H, d, J=8.0Hz), 7.33(2H, d, J=8.6Hz), 7.42(2H, d, J=8.6Hz).

FAB-Mass: 341 (MH+).

Example 7: Synthesis of 1-[1-(2-fluorophenethyl)piperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (300 mg) and 2-

as the one of Production Example 1 were treated as in Example 2 to give the hydrochloride (290 mg) of the title compound as a white powder (yield: 54%).

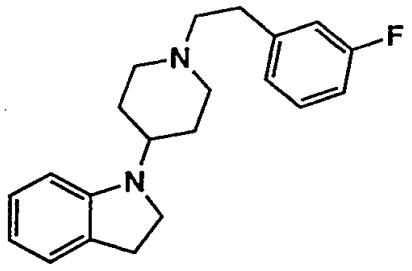
m.p. (hydrochloride): 229 - 231°C.

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.81-1.90(2H, m), 2.00-2.12(2H, m), 2.89(2H, t, J=8Hz), 3.01-3.16(4H, m), 3.20-3.30(2H, m), 3.33(2H, t, J=8Hz), 3.60-3.79(3H, m), 6.53-6.60(2H, m), 6.96-7.04(2H, m), 7.16-7.23(2H, m), 7.29-7.40(2H, m), 10.80(1H, br-s).

FAB-Mass: 325(MH+).

Example 8: Synthesis of 1-[1-(3-fluorophenethyl)piperidin-4-yl]indoline



Dicyclohexylcarbodiimide (560 mg) was added to a solution of 1-(piperidin-4-yl)indoline (500 mg) in methylene chloride (30 ml) followed by stirring at 0°C. After 1 hr, 3-fluorophenylacetic acid (420 mg) was added thereto and the resultant mixture was stirred at room temperature for 2 hr. The crystalline precipitates were filtered off and the filtrate was concentrated under reduced pressure and purified by silica gel

column chromatography (hexane/ethyl acetate system). The residue was diluted with tetrahydrofuran (30 ml). Next, lithium aluminum hydride (290 mg) was added in portions thereto under ice cooling and stirring and the resultant mixture was stirred at room temperature overnight. Under ice cooling, water (0.29 ml), a 5 N aqueous solution (0.87 ml) of sodium hydroxide and further water (0.29 ml) were carefully added dropwise into the reaction solution followed by vigorous stirring. The resulting precipitate was filtered off and the filtrate was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate system). Then the obtained product was converted into a hydrochloride in a conventional manner to give the hydrochloride (550 mg) of the title compound as a white powder (yield: 61%).

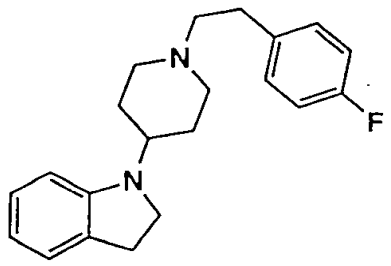
m.p. (hydrochloride): 231 - 234°C.

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.81-1.89(2H, m), 1.93-2.07(2H, m), 2.88(2H, t, J=8Hz), 3.00-3.11(4H, m), 3.23-3.35(4H, m), 3.58-3.75(3H, m), 6.51-6.57(2H, m), 6.95-7.03(2H, m), 7.06-7.19(2H, m), 7.35-7.41(2H, m).

FAB-Mass: 325(MH+).

Example 9: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]indoline



A 2.5 M solution (0.36 ml) of n-butyllithium in hexane was added dropwise over 10 min into a solution of 1-[1-(4-fluorophenethyl)piperidin-4-yl]-6-bromoindoline (300 mg) in tetrahydrofuran (15 ml) at -78°C. After 10 min, the resultant mixture was mixed with a saturated aqueous solution of ammonium chloride and ethyl acetate and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and purified by silica gel column chromatography (methylene chloride/ethanol system). Then the obtained product was converted into the hydrochloride in a conventional manner to give the hydrochloride (240 mg) of the title compound as white needles (yield: 90%).

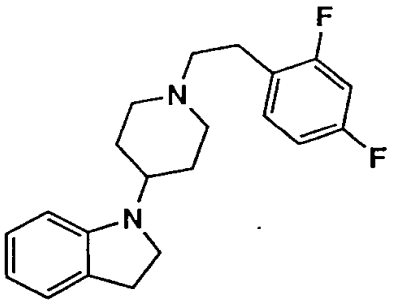
m.p. (hydrochloride): 233°C (decomp.).

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.81-1.90(2H, m), 2.00-2.13(2H, m), 2.90(2H, t, J=8Hz), 3.00-3.14(4H, m), 3.19-3.28(2H, m), 3.30(2H, t, J=8Hz), 3.58-3.63(2H, m), 3.69-3.79(1H, m), 6.51-6.60(2H, m), 6.94-7.08(2H, m), 7.12-7.20(2H, m), 7.29-7.39(2H, m), 10.70(1H, br-s).

FAB-Mass: 325(MH+).

Example 10: Synthesis of 1-[1-(2,4-difluorophenethyl)-piperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (500 mg) and 2,4-difluorophenylacetic acid (470 mg) were treated as in Example 8 to give the hydrochloride (720 mg) of the title compound as a white powder (yield: 76%).

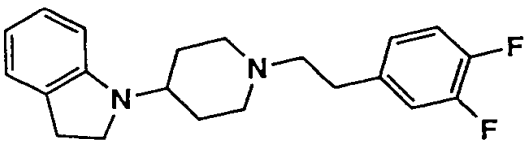
m.p. (hydrochloride): 226 - 227°C.

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.81-2.08(4H, m), 2.89(2H, t, J=8Hz), 3.00-3.15(4H, m), 3.20-3.39(4H, m), 3.40-3.75(3H, m), 6.49-6.57(2H, m), 6.94-7.04(2H, m), 7.07-7.12(1H, m), 7.23-7.30(1H, m), 7.39-7.46(1H, m).

FAB-Mass: 343(MH+).

Example 11: Synthesis of 1-[1-(3,4-difluorophenethyl)-piperidin-4-yl]indoline



3,4-Difluorophenylacetic acid (0.095 g) was dissolved in tetrahydrofuran (5.0 ml). After adding 1,1-carbonyldiimidazole (0.089 g) to the resultant solution, the resultant mixture was stirred at room temperature for 15 min followed by the addition of 1-(piperidin-4-yl)indoline (0.1 g). After stirring at room temperature overnight, the resultant mixture was diluted with ethyl acetate, washed with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give a colorless oil. Then this product was dissolved in tetrahydrofuran (2.5 ml) and lithium aluminum hydride (0.046 g) was added thereto under ice cooling followed by heating under reflux for 2 hr. After cooling the reaction solution, water (0.05 ml), a 5 N aqueous solution (0.05 ml) of sodium hydroxide and further water (0.15 ml) were added thereto. The precipitated solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.190 g) as a colorless oil (yield: quantitative).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride (0.120 g) of the title compound was obtained.

m.p. (hydrochloride): 223°C.

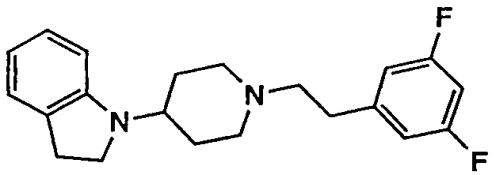
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.87(2H, br-d), 2.06(2H, m), 2.90(2H, t, J=8.4Hz), 3.09(4H, m), 3.28(2H, m), 3.33(2H, t, J=8.4Hz), 3.62(2H, br-d), 3.74(1H, br-t), 6.57(1H, d, J=7.0Hz), 6.58(1H, t, J=7.0Hz), 7.01(1H, t, J=7.0Hz), 7.04(1H, d, J=7.0Hz), 7.16(1H, m), 7.39-7.46(2H, m).

FAB-Mass: 343(MH+).

Example 12: Synthesis of 1-[1-(3,5-difluorophenethyl)-piperidin-4-yl]indoline



3,5-Difluorophenylacetic acid (0.189 g) was treated as in Example 11 to give the title compound (0.342 g) as a colorless oil (yield: quantitative).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride (0.268 g) of the title compound was obtained.

m.p. (hydrochloride): 208°C.

Hydrochloride

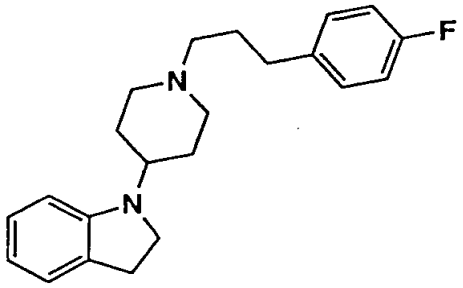
^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.89(2H, br-d), 2.12(2H, m), 2.92(2H, t, J=8.2Hz),

3.09(4H, m), 3.27(2H, m), 3.36(2H, t, J=8.2Hz), 3.61(2H, br-d), 3.78(1H, m), 6.64(1H, d, J=8.0Hz), 6.64(1H, t, J=8.0Hz), 7.04(1H, t, J=8.0Hz), 7.07(1H, d, J=8.0Hz), 7.14-7.18(1H, m), 7.38-7.45(2H, m).

FAB-Mass: 343(MH+).

Example 13: Synthesis of 1-[1-(4-fluorophenylpropyl)-piperidin-4-yl]indoline



Ethanol (50 ml) was added to 4-fluorocinnamic acid (5 g) and then ethyl acetate was further added thereto to dissolve completely. After adding a palladium carbon catalyst, catalytic reduction was carreid out under atmospheric pressure. Then the reaction mixture was filtered through celite and the filtrate was concentrated under reduced pressure. A portion (0.082 g) of the resulting colorless crystals was dissolved in tetrahydrofuran (5.0 ml), and carbonyldiimidazole (0.079 g) and 1-(4-piperidyl)indoline (0.1 g) were added thereto followed by stirring at room temperature for 14 hr. Then the reaction solution was diluted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and concentrated under

reduced pressure to give a pale yellow oily substance (0.171 g). This product was dissolved in tetrahydrofuran (5.0 ml) and lithium aluminum hydride (0.046 g) was added thereto under ice cooling. After heating under reflux for 2 hr, the reaction mixture was ice cooled again and water (0.05 ml), a 5 N aqueous solution (0.05 ml) of sodium hydroxide and further water (0.15 ml) were added thereto. The resulting solid was filtered off and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.113 g) as a colorless oil (yield: 68.1%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride (hygroscopic) of the title compound was obtained.

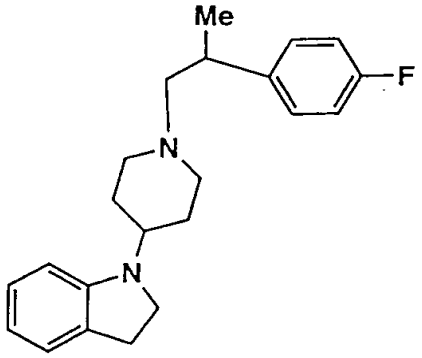
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.83(2H, br-d), 1.97-2.14(4H, m), 2.64(2H, t, J=8.0Hz), 2.90(2H, t, J=8.0Hz), 3.00(4H, m), 3.33(2H, t, J=8.4Hz), 3.54(2H, br-d), 3.73(1H, m), 6.58(1H, d, J=7.6Hz), 6.61(1H, t, J=7.6Hz), 7.02(1H, t, J=7.6Hz), 7.05(1H, d, J=7.6Hz), 7.14(2H, t, J=8.8Hz), 7.29(2H, dd, J=5.6, 8.8Hz).

ESI-Mass: 339.2(MH+).

Example 14: Synthesis of 1-{1-[2-(4-fluorophenyl)propyl]piperidin-4-yl}indoline



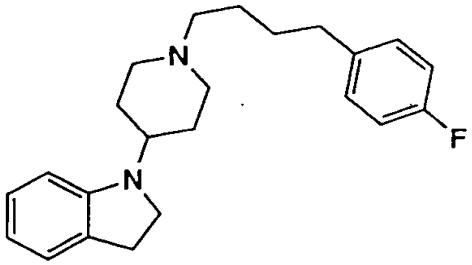
1-(4-Piperazinyl)indoline (0.20 g) was dissolved in dimethylformamide (3 ml) and 4-(2-bromo-1-methylethyl)fluorobenzene (10.0 g) and triethylamine (0.14 ml) were added to the resultant solution followed by stirring at 60°C overnight. After adding water, the liquid reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After evaporating the solvent, the resulting residue was purified by NH-silica gel column chromatography (methanol/methylene chloride system) to give the title compound (178 mg) as an oil.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.37(3H, d, J=6.8Hz), 1.60-2.10(8H, m), 2.85-3.50(8H, m), 6.36(1H, d, J=7.5Hz), 6.58(1H, t, J=7.5Hz), 6.97-7.07(4H, m), 7.24-7.30(2H, m).

FAB-Mass: 339(MH+).

Example 15: Synthesis of 1-[1-(4-fluorophenylbutyl)piperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (1.0 g) and 4-(4-fluorophenyl)butyric acid (0.9 g) were treated as in Example 8 to give the hydrochloride (0.23 g) of the title compound as a white powder (yield: 12%).

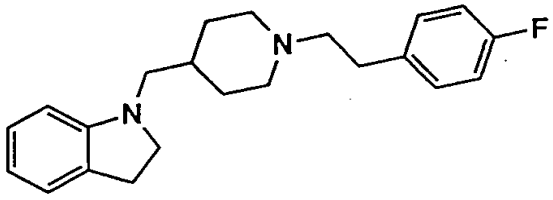
m.p. (hydrochloride): 204 - 206°C.

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.51-1.71(4H, m), 1.79-1.86(2H, m), 1.89-2.02(2H, m), 2.60(2H, t, J=7Hz), 2.87(2H, t, J=8Hz), 2.92-3.07(4H, m), 3.29(2H, t, J=7Hz), 3.47-3.53(2H, m), 3.62-3.72(1H, m), 6.48-6.56(2H, m), 6.92-7.02(2H, m), 7.06-7.12(2H, m), 7.20-7.28(2H, m), 9.99(1H, br-s).

FAB-Mass: 353(MH+).

Example 16: Synthesis of 1-[1-(4-fluorophenethyl)piperidin-4-yl]methylindoline



1-Fluorophenethyl-4-formylpiperidine (0.240 g) and indoline (0.095 ml) were dissolved in 1,2-dichloroethane (3.5

ml). After successively adding acetic acid (0.29 ml) and triacetoxylated sodium borohydride (0.36 g), the resultant mixture was stirred at room temperature for 2 hr. Then it was mixed with a saturated aqueous solution of sodium bicarbonate and ethyl acetate and the layers were separated. The organic layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.211 g) as a yellow oil (yield: 73.3%).

Next, oxalic acid (28 mg) was added to the product to give a salt followed by recrystallization from acetone. Thus, the oxalate of the title compound was obtained as colorless crystals.

m.p. (oxalate): 201 - 206°C.

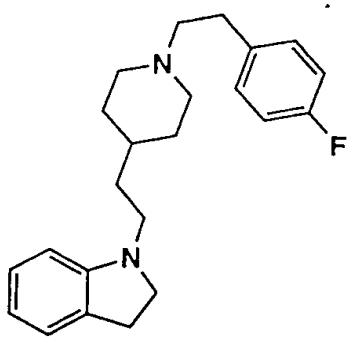
Oxalate

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.57(2H, m), 1.90(1H, m), 1.95(2H, m), 2.92(6H, m), 3.07(2H, m), 3.23(2H, m), 3.34(2H, t, J=8.4Hz), 3.57(2H, br-d), 6.52(1H, d, J=7.6Hz), 6.58(1H, t, J=7.6Hz), 6.99(1H, t, J=7.6Hz), 7.03(1H, d, J=7.6Hz), 7.18(2H, t, J=8.8Hz), 7.33(2H, dd, J=5.2, 8.8Hz).

ESI-Mass: 339.1(MH+).

Example 17: Synthesis of 1-{2-[1-(4-fluorophenethyl)piperidin-4-yl]ethyl}indoline



Indoline (170 mg), 1-(4-fluorophenethyl)-4-piperidinacetaldehyde (360 mg), acetic acid (440 mg) and triacetoxylated sodium borohydride (490 mg) were treated as in Example 1 to give the hydrochloride (270 mg) of the title compound as white prisms (yield: 48%).

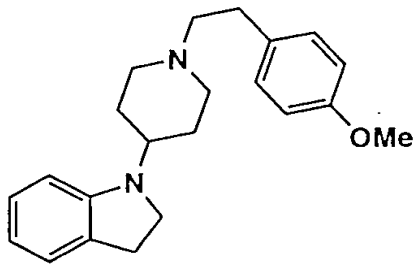
m.p. (hydrochloride): 159 - 161°C.

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.45-1.70(5H, m), 1.89-1.98(2H, m), 2.80-3.10(8H, m), 3.14-3.36(4H, m), 3.50-3.58(2H, m), 6.50-6.58(2H, m), 6.96-7.03(2H, m), 7.16-7.21(2H, m), 7.30-7.38(2H, m), 10.16(1H, m).

FAB-Mass: 353(MH+).

Example 18: Synthesis of 1-[1-(4-methoxyphenethyl)piperidin-4-yl]indoline



4-Methoxyphenethyl bromide (0.23 g) was treated as in Example 2 to give the title compound (0.131 g) as colorless crystals (yield: 86.1%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride of the title compound was obtained as colorless crystals.

m.p. (hydrochloride): 244°C.

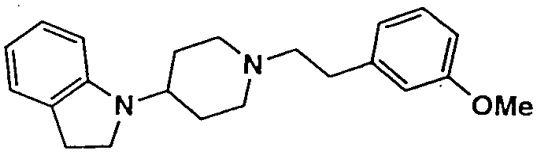
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.88(2H, m), 2.02(2H, m), 2.90(2H, t, J=8.4Hz), 3.00(2H, m), 3.10(2H, m), 3.21(2H, m), 3.33(2H, t, J=8.4Hz), 3.63(2H, br-d), 3.73(3H, s), 3.74(1H, m), 6.57(1H, d, J=7.6Hz), 6.59(1H, t, J=7.6Hz), 6.91(2H, d, J=8.4Hz), 7.01(1H, t, J=7.6Hz), 7.04(1H, d, J=7.6Hz), 7.21(2H, d, J=8.4Hz).

FAB-Mass: 337(MH+).

Example 19: Synthesis of 1-[1-(3-methoxyphenethyl)piperidin-4-yl]indoline



3-Methoxyphenethyl alcohol was treated as in Production Example 1. Then the pale yellow oily substance (0.23 g) thus obtained was treated as in Example 2 to give the title compound (0.150 g) as colorless crystals (yield: 45.4%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride of the title compound was obtained as colorless crystals.

m.p. (hydrochloride): 229°C.

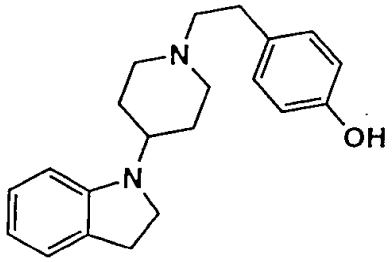
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.88(2H, br-d), 2.14(2H, m), 2.92(2H, t, J=8.4Hz), 3.07(4H, m), 3.25(2H, m), 3.37(2H, t, J=8.4Hz), 3.63(2H, br-d), 3.75(3H, s), 3.77(1H, m), 6.57(1H, d, J=7.6Hz), 6.45(1H, m), 6.81-6.88(3H, m), 7.05(2H, m), 7.26(1H, d, J=8.0Hz).

FAB-Mass: 337(MH+).

Example 20: Synthesis of 1-[1-(4-hydroxyphenethyl)piperidin-4-yl]indoline



1-[1-(4-Methoxyphenethyl)piperidin-4-yl]indoline (0.23 g) was dissolved in a 47% aqueous solution (5 ml) of hydrobromic acid and the resultant solution was heated under reflux for 90 min. After allowing to cool, the resultant mixture was poured into a saturated aqueous solution of sodium bicarbonate (pH 9 - 10), extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by NH-silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.113 g) as colorless crystals (yield: 75.7%).

Next, hydrochloric acid was added to the product to give a salt followed by recrystallization from ethanol. Thus, the hydrochloride of the title compound was obtained as colorless crystals.

m.p. (hydrochloride): 240°C.

Hydrochloride

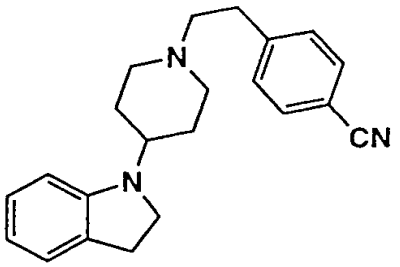
^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.87(2H, m), 2.09(2H, m), 2.91(2H, t, J=8.4Hz), 2.95(2H, m), 3.07(2H, m), 3.18(2H, m), 3.34(2H, t, J=8.4Hz), 3.62(2H, br-d), 3.75(1H, m), 6.61(2H, m), 6.73(2H, d, J=8.4Hz),

7.05(4H, m), 10.69(1H, br-s).

FAB-Mass: 323(MH+).

Example 21: Synthesis of 1-[1-(4-cyanophenethyl)piperidin-4-yl]indoline



1-[1-(4-Hydroxyiminomethylphenethyl)piperidin-4-yl]indoline (0.466 g) was dissolved in methylene chloride (6.5 ml) and triethylamine (0.35 ml) was added thereto. In a nitrogen atmosphere at -78°C, trifluoroacetic anhydride (0.14 ml) was added dropwise into the resultant solution followed by stirring for 3 hr. After adding a saturated aqueous solution of sodium bicarbonate, the resultant mixture was extracted with ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methylene chloride/methanol system) to give the title compound (0.126 g) as a pale yellow oil (yield: 28.9%).

Next, hydrochloric acid was added to the product to give a salt. Thus, the hydrochloride of the title compound was obtained.

m.p. (hydrochloride): 228°C.

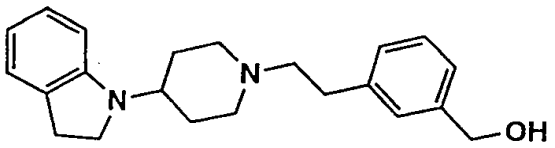
Hydrochloride

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.89(2H, br-d), 2.12(2H, m), 2.91(2H, t, J=8.4Hz), 3.12(2H, m), 3.21(2H, m), 3.28(2H, m), 3.34(2H, t, J=8.4Hz), 3.63(2H, br-d), 3.76(1H, m), 6.60(1H, d, J=7.4Hz), 6.61(1H, t, J=7.4Hz), 7.02(1H, t, J=7.4Hz), 7.05(1H, d, J=7.4Hz), 7.52(2H, d, J=8.0Hz), 7.84(2H, d, J=8.0Hz).

FAB-Mass: 332(MH+).

Example 22: Synthesis of 1-[1-(3-hydroxymethylphenethyl)piperidin-4-yl]indoline



3-(t-Butyl)dimethylsilyloxymethylphenethyl bromide (0.22 g) was treated as in Example 2 to give the title compound (0.116 g) as a pale yellow oil (yield: 31.9%).

Free

^{1}H-NMR (400 MHz, $CDCl_3$):

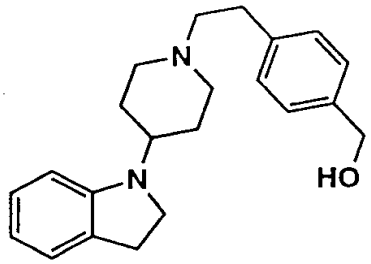
δ(ppm) 1.75-1.84(4H, m), 2.15(2H, m), 2.63(2H, m), 2.84(2H, m), 2.95(2H, t, J=8.4Hz), 3.14(2H, br-t), 3.37(1H, m), 3.39(2H, t, J=8.4Hz), 4.68(2H, s), 6.39(1H, d), 6.60(1H, t), 7.03(2H, m), 7.12-7.35(4H, m).

Next, hydrochloric acid (0.372 g) was added to the product to give a salt followed by recrystallization from ethanol-

acetone mixtures. Thus, the hydrochloride of the title compound was obtained.

m.p.: 218°C.

Example 23: Synthesis of 1-[1-(4-hydroxymethylphenethyl)piperidin-4-yl]indoline



4-(2-Bromoethyl)benzyl alcohol (0.2 g) was treated as in Example 2 to give the title compound (0.177 g) as a pale yellow oil (yield: 53.7%).

Free

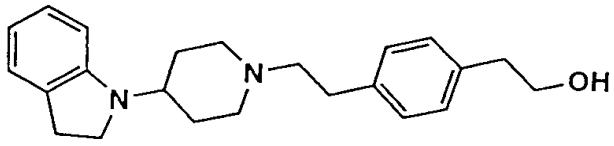
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.79(4H, m), 2.12(2H, dt, J=2.8, 11.6Hz), 2.59(2H, m), 2.81(2H, m), 2.94(2H, t, J=8.4Hz), 3.12(2H, br-d), 3.38(2H, t, J=8.4Hz), 3.40(1H,m), 4.65(2H, s), 6.42(1H, d, J=8.0Hz), 6.61(1H, t, J=8.0Hz), 7.03(1H, t, J=8.0Hz), 7.05(1H, d, J=8.0Hz), 7.21(2H, d, J=8.0Hz), 7.49(2H, d, J=8.0Hz), 8.11(1H, s).

Next, hydrochloric acid was added to the product to give the hydrochloride of the title compound.

FAB-Mass; 337 (MH+).

Example 24: Synthesis of 1-{1-[4-(2-hydroxyethyl)phenethyl]piperidin-4-yl}indoline



4-[2-(t-Butyldimethylsilyloxy)ethyl]phenethyl bromide (0.2 g) was treated as in Example 2 to give a pale yellow oil (0.113 g). Then this product was dissolved in tetrahydrofuran (1.0 ml). To the resultant solution was added a 2.0 M solution (0.49 ml) of tetrabutylammonium fluoride in tetrahydrofuran and the resultant mixture was stirred at room temperature for 1.5 hr. The liquid reaction mixture was concentrated under reduced pressure to give the title compound (0.086 g) as a yellow oil (yield: quantitative).

Free

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.88(4H, m), 2.31(2H, m), 2.75(2H, m), 2.85(2H, t, J=6.4Hz), 2.95(2H, t, J=8.4Hz), 3.21(2H, m), 3.24(2H, m), 3.40(2H, t, J=8.4Hz), 3.85(2H, t, J=6.4Hz), 6.41(1H, d), 6.60(1H, t), 7.03(2H, m), 7.18(4H, s).

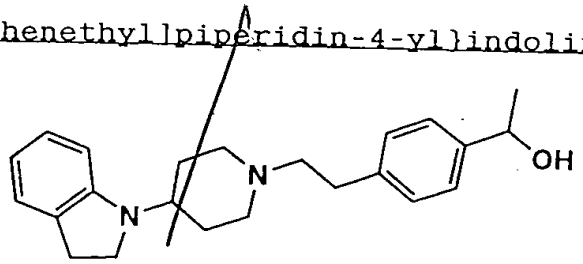
Then oxalic acid (0.372 g) was added to the above product to give the oxalate as a brown oil.

FAB-Mass: 351 (MH+).

Example 25: Synthesis of 1-{4-[(1-

hydroxyethyl]phenethyl]piperidin-4-yl}indoline

A10



4-(1-Hydroxyethyl)phenethyl bromide (0.2 g) was treated as in Example 2 to give the title compound (0.044 g) as a yellow oil (yield: 12.6%).

Then oxalic acid (11 mg) was added to the above product to give a salt followed by recrystallization from ethanol to give the oxalate.

m.p. (oxalate): 132°C.

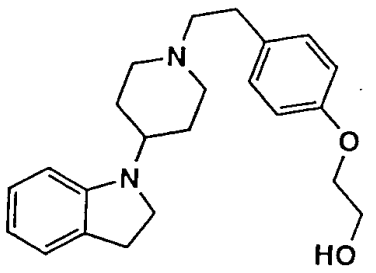
Oxalate

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.30(3H, d, J=6.4Hz), 1.86(4H, m), 2.88(2H, t, J=8.0Hz), 2.92(4H, m), 3.15(2H, m), 3.32(2H, t, J=8.4Hz), 3.54(2H, m), 3.67(1H, m), 4.69(1H, q, J=6.7Hz), 6.51(1H, d, J=8.0Hz), 6.55(1H, t, J=8.0Hz), 6.99(1H, t, J=8.0Hz), 7.02(1H, d, J=8.0Hz), 7.22(2H, d, J=8.0Hz), 7.30(1H, d, J=8.0Hz).

FAB-Mass: 351(MH+).

Example 26: Synthesis of 1-{1-[4-(2-hydroxyethoxy)phenethyl]piperidin-4-yl}indoline



N,N-Dimethylformamide (2.5 ml) was added to 1-[1-(4-hydroxyphenethyl)piperidin-4-yl]indoline (0.1 g), potassium carbonate (0.081 g) and 1-bromo-2-di(t-butyl)dimethylsilyloxyethane (0.20 g) and the resultant mixture was heated and stirred at 80°C for 28 hr. After allowing to cool, it was extracted with ethyl acetate (200 ml), washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give a colorless oil. Then this product was dissolved in tetrahydrofuran (1.3 ml) and a 2.0 M solution (0.88 ml) of tetrabutylammonium fluoride in tetrahydrofuran was added thereto followed by stirring the mixture at room temperature for 1 hr. The resultant mixture was extracted with ethyl acetate (200 ml), washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (0.124 g) as a colorless oil (yield: 69.0%).

Free

^{1}H-NMR (400 MHz, $CDCl_3$):

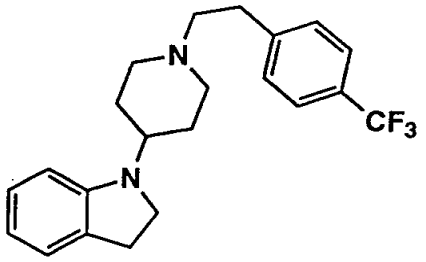
δ(ppm) 1.80(4H, m), 2.11(2H, dt, J=3.2, 11.6Hz), 2.58(2H, m), 2.76(2H, m), 2.94(2H, t, J=8.4Hz), 3.12(2H, br-d), 3.39(2H, t, J=8.4Hz), 3.40(1H, m), 3.94(2H, t, J=8.4Hz), 4.06(2H, t, J=8.4Hz), 6.40(1H, d, J=7.6Hz), 6.60(1H, t, J=7.6Hz), 6.85(2H, d, J=8.4Hz), 7.04(2H, m), 7.13(2H, d, J=8.4Hz).

ESI-Mass: 367.2(MH+).

Next, hydrochloric acid was added to the above product to give the hydrochloride of the title compound as colorless crystals.

m.p. (hydrochloride): 229°C.

Example 27: Synthesis of 1-[1-(4-trifluoromethylphenethyl)piperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (1.0 g) and 4-trifluoromethylphenylacetic acid (1.0 g) were treated as in Example 8 to give the hydrochloride (0.98 g) of the title compound as a white powder (yield: 48%).

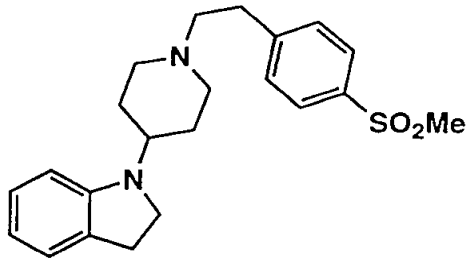
m.p. (hydrochloride): 212°C (decomp.).

^{1}H-NMR (400 MHz, DMSO-d_6):

δ(ppm) 1.81-1.89(2H, m), 1.94-2.09(2H, m), 2.88(2H, t, J=8Hz), 3.02-3.20(4H, m), 3.28-3.36(4H, m), 3.60-3.79(3H, m), 6.52-6.58(2H, m), 6.96-7.04(2H, m), 7.53(2H, d, J=8Hz), 7.72(2H, d, J=8Hz).

FAB-Mass: 375(MH+).

Example 28: Synthesis of 1-[1-(4-methanesulfonylphenethyl)piperidin-4-yl]indoline



1-(Piperidin-4-yl)indoline (200 mg) and 4-methanesulfonylphenethyl bromide (290 mg) were treated as in Example 2 to give the title compound (180 mg) as a white powder (yield: 43%).

m.p. (hydrochloride): 208 - 210°C.

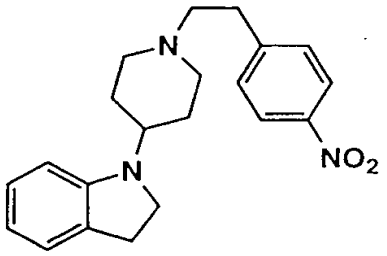
^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.69-1.86(4H, m), 2.10-2.18(2H, m), 2.61-2.67(2H, m), 2.87-2.98(4H, m), 3.04(3H, s), 3.06-3.14(2H, m), 3.35-3.44(3H, m), 6.41(1H, d, J=8Hz), 6.60(1H, t, J=8Hz), 7.01-7.06(2H, m), 7.41(2H, d, J=8Hz), 7.85(2H, d, J=8Hz).

FAB-Mass: 385(MH+).

Example 29: Synthesis of 1-[1-(4-nitrophenethyl)piperidin-

4-yl]indoline



1-(Piperazin-4-yl)indoline (2.00 g) was dissolved in dimethylformamide (20 ml) and 4-(2-bromoethyl)nitrobenzene (10.0 g) and triethylamine (2.9 ml) were added thereto followed by stirring the resultant mixture at 100°C overnight. After adding water to the reaction solution, extracted with ethyl acetate, the organic layer was washed with brine and dried over magnesium sulfate. After distilling off the solvent, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.05 g) as a slightly yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$):

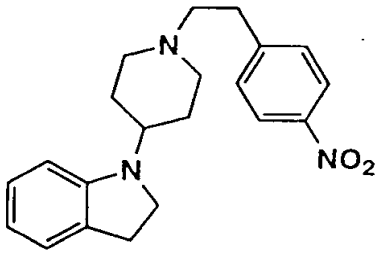
δ(ppm) 1.70-1.90(4H, m), 2.14-2.22(2H, m), 2.64-2.72(4H, m), 2.90-3.00(2H, m), 3.08-3.16(2H, m), 3.36-3.46(3H, m), 6.41(1H, d, J=7.6Hz), 6.61(1H, d, J=7.6Hz), 7.02-7.08(2H, m), 7.35-7.40(2H, m), 8.13-8.18(2H, m).

FAB-Mass: 352(MH+).

m.p.: 95 - 97°C.

Example 30: Synthesis of 1-[1-(4-aminophenethyl)piperidin-4-yl]indoline

4-yl]indoline



1-(Piperazin-4-yl)indoline (2.00 g) was dissolved in dimethylformamide (20 ml) and 4-(2-bromoethyl)nitrobenzene (10.0 g) and triethylamine (2.9 ml) were added thereto followed by stirring the resultant mixture at 100°C overnight. After adding water to the reaction solution, extracted with ethyl acetate, the organic layer was washed with brine and dried over magnesium sulfate. After distilling off the solvent, the obtained residue was purified by silica gel column chromatography (hexane/ethyl acetate system) to give the title compound (1.05 g) as a slightly yellow solid.

^{1}H-NMR (400 MHz, $CDCl_3$):

δ(ppm) 1.70-1.90(4H, m), 2.14-2.22(2H, m), 2.64-2.72(4H, m), 2.90-3.00(2H, m), 3.08-3.16(2H, m), 3.36-3.46(3H, m), 6.41(1H, d, J=7.6Hz), 6.61(1H, d, J=7.6Hz), 7.02-7.08(2H, m), 7.35-7.40(2H, m), 8.13-8.18(2H, m).

FAB-Mass: 352(MH+).

m.p.: 95 - 97°C.

Example 30: Synthesis of 1-[1-(4-aminophenethyl)piperidin-4-yl]indoline